EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Restaysis

International non-proprietary name: ciclosporin

Procedure No. EMEA/H/C/004229/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ANOVA	analysis of variance
BID	Twice-daily
CD147	Cluster of differentiation
CFS	Corneal fluorescein staining
CGC	Conjunctival goblet cell
CHMP	Committee for Medicinal Products for Human Use
COE	Ciclosporin ophthalmic emulsion
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CsA	Ciclosporin A
DED	Dry eye disease
DEWS	International Dry Eye Workshop
EAG	External Advisory Group
EMA	European Medicines Agency
EU	European Union
GEE	Generalized estimating equation
GP	General Practitioner
IL-2	Interleukin-2
HLA-DR	Human Leukocyte Antigen - antigen D-Related
ITF	International Task Force (ITF) Delphi Panel on Dry Eye
ITT	Intent-to-Treat
KCS	Keratoconjunctivitis sicca
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency (Sweden
NDS	New Drug Submission (Health Canada marketing application)
NFAT	Nuclear factor of activated T cells
NON-W	Notice of NonCompliance Withdrawal
OSDI	Ocular surface disease index
PK	Pharmacokinetics
SAE	Serious adverse event
SOC	System Organ Class
TBUT	Tear film break-up time
US	United States

1. Recommendation

Based on the review of the data on quality, safety, efficacy and risk management plan and the Applicant's written responses to the CHMP LoOI, the CHMP considers that the application for Restaysis in the treatment of moderate dry eye disease in adult patients, including those with Sjögren's disease, which is inadequately controlled despite treatment with tear substitutes or ocular lubricants, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Evidence of efficacy has not been established. The concerns about the design of the retrospective analysis remain and the effects estimated therefrom, in particular the estimated effects on endpoints other than those related to staining are not accepted as being reliable. The Applicant is requested to provide a consolidation of all ocular staining data from the three pivotal studies – in which total, corneal and conjunctival staining should be distinguished. This should be presented both as data from individual studies and as a pooled analysis, for all treatment arms (0.05% COE, 0.1% COE and vehicle) and separately for moderate and severe DED patients. The scientific basis of the staining methods used and the clinical relevance of the estimated treatment effects obtained should be fully discussed and substantiated by external data where available.

Inspection issues

None.

New active substance status

Ciclosporin is not to be qualified as a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Restaysis is indicated for the treatment of moderate dry eye disease in adults.

DED is classed as aqueous tear deficient or evaporative, according to aetiology, although there is overlap in the clinical manifestation and one can lead to the other once the disease is established.

2.1.2. Epidemiology and risk factors

The prevalence of dry eye ranges from 5%-15% in the USA, Australia, and Europe to 30-50% in Asia Some of the risk factors for DED include older age, peri- and postmenopausal women and patients receiving hormone replacement therapy, diet low in omega-3 and omega-6 fatty acids, medications (antihistamines, diuretics, psychotropics, cholesterol-lowering agents), refractive surgery, including LASIK, radiation therapy, computer use, contact lens wear, autoimmune disease, atopy.

2.1.3. Aetiology and pathogenesis

Aqueous tear-deficient dry eye (ADDE) results primarily from deficient lacrimal secretion (DEWS, 2007a). Aqueous tear-deficient dry eye includes dry eye from autoimmune Sjögren's syndrome and non-Sjögren's DED. Evaporative DED arises from intrinsic variables such as disorders of lid aperture or low-blink rate, or poor tear quality, leading to a higher rate of evaporation, for example due to Meibomian gland dysfunction.

Regardless of the initiating factors or groups of factors, tear hyperosmolarity is a common final pathway that leads to ocular surface damage and can set in train a cycle of injury-inflammation-injury. Eventually, patients can develop a self-sustaining DED with an unstable and poorly maintained tear film which may develop into more severe forms of DED. Inflammation has a prominent role in the development and amplification of both the signs and symptoms of the disease.

DED, especially in older adults, most often results from several aetiologies.

2.1.4. Clinical presentation, diagnosis and stage

In 2007, the DEWS developed an updated version of the classification presented in the National Eye Institute/Industry Workshop Report in 1995. Dry eye disease is classified based on both the severity of the disease and the etiology. DEWS defined a DED severity classification system with 4 levels of increasing disease severity based on both symptoms and signs of DED (DEWS, 2007a). The DEWS 4-tiered list of DED treatment recommendations was established to tailor treatment strategy on DED severity level (DEWS, 2007b); Level 1 mild; Levels 2 and 3 moderate; Level 4 severe

2.1.5. Management

The treatment of DED aims at both improving disease signs and symptoms and depends on the severity of the disease. Most patients with mild-to-moderate DED can be treated symptomatically with lubricants/artificial tears for long periods of time. Other therapeutic strategies include ocular inserts, occlusion of the lacrimal puncta, and anti-inflammatory treatment. According to DEWS, patients with moderate to severe DED are recommended to start using topical anti-inflammatory drugs such as steroids and ciclosporin. However, long-term use of corticosteroids eye drops is associated with an increased risk of side effects such as intraocular hypertension, ocular infections and cataract.

Ciclosporin formulations, from 0.05% to 2% ophthalmic emulsions in olive or castor oil, up to four times daily, have been used in clinical practice as an alternative to steroids in severe forms of DED for several decades. A 0.1% ophthalmic ciclosporin formulation (Ikervis) was approved in the EU in January 2015 for treatment of severe keratitis in association with dry eye disease. Restasis (0.05% ciclosporin) is marketed in 30 countries worldwide. In the USA, a 0.05% ciclosporin ophthalmic emulsion (Restasis) is available to increase tear production in patients with ocular inflammation associated with keratoconjunctivitis sicca. Restasis is available in some EU countries under compassionate use programs. In other countries, pharmacy compounded oily ciclosporin formulations are used.

An unmet need is recognised in moderate DED.

2.2. About the product

Restaysis - ciclosporin (CsA) ophthalmic emulsion 0.05% (COE 0.05%) - is an immunomodulator belonging to the therapeutic class of ophthalmologicals (S01XA18).

Restaysis is presented as a sterile, preservative-free eye drop emulsion in single use containers.

A revised indication is proposed following the Day 120 List of Questions:

Restaysis is indicated for the treatment of adult patients with moderate dry eye disease which is not adequately controlled despite treatment with tear substitutes.
The recommended dosage is one drop instilled twice a day in each eye approximately 12 hours apart.

Restaysis is restricted for supply on prescription by a specialist ophthalmology practitioner.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

Two prior marketing authorisation applications have been submitted in the European Union for RESTASIS (proposed new invented name of RESTAYSIS in the EU). An MAA was first submitted in December 1999 via the centralised procedure for "treatment of moderate and severe keratoconjunctivitis sicca (chronic dry eye disease)" (EMEA/H/C/346). A second MAA was submitted in 2008 via the decentralised procedure to "increase tear production in patients with keratoconjunctivitis sicca inadequately controlled with artificial tears," (FR/H/349/01/DC). Both applications were withdrawn prior to conclusion of the respective procedures due to concern over inadequate demonstration of efficacy.

Outside the EU, RESTASIS is currently approved and marketed in over 30 countries including the US and Canada. In the US, RESTASIS was approved in 2002 with the indication "to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca". RESTASIS was approved in Canada in 2010 for "the treatment of moderate to moderately severe (level 2 to 3 severity by DEWS Guidelines) aqueous deficient dry eye disease, characterized by moderate to moderately severe: ocular staining, reduction in tear production and fluctuating visual symptoms, such as blurred vision". The Canadian approval was based on a re-analysis of a subgroup of DEWS level 2 to 3 patients from 3 pivotal studies (192371-002, -003, and -501). A retrospective analysis of the same pooled subpopulation of moderate DED (DEWS level 2-3) forms the principal basis of the current dossier in the EU.

The applicant received CHMP (Procedure No.: EMEA/H/SA/3167/1/2015/II) and MPA (Sweden; Dnr 4.2.3-2014-079186) scientific advice in 2015 regarding clinical development. During scientific advice it was stressed that the Canadian External Advisory Group convened to advise on the design and conduct of the re-analysis should be independent and not influenced by the Company.

2.4. General comments on compliance with GMP, GLP, GCP

There are no GMP or GLP issues. Although the submitted clinical studies are formally compliant with GCP, there is concern that the interpretation of data from these has been heavily biased by prior knowledge.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

  The application for marketing authorisation is made under Article 3(2) of Regulation (EC) No 726/2004 (Optional scope), Annex 3(2)(b) when significant innovation or interest to patients at EU level is considered to apply.

- Accelerated procedure

Not applicable

- Conditional approval

  Not applicable

- Exceptional circumstances

  Not applicable

- Biosimilar application

  Not applicable

- 1 year data exclusivity

  Not applicable

- Significance of paediatric studies

  Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Restaysis eye drops is a white, opaque to slightly translucent, sterile, preservative-free and isotonic, oil-in-water emulsion containing Ciclosporin as a drug substance at a concentration of 0.05%. The inactive ingredients are castor oil polysorbate 80, carbomer copolymer type A, glycerine, sodium hydroxide, and purified water. The eye drops, emulsion is presented in colourless low density polyethylene unit-dose vials (0.4 mL fill volume in a 0.9 mL fill capacity).

3.1.2. Active Substance

The drug substance is supported by EDQM certificates of suitability and meets the requirement of the monograph for ciclosporin Ph. Eur.

The CEPs Holders have declared the absence of use of material of human or animal origin in the manufacture of the active substance. This is reflected in the EDQM CEP submitted.

The control tests and specifications for drug substance product are adequately drawn up.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Restaysis 0.5 mg/ml eye drops, emulsion is a sterile, preservative-free emulsion containing the drug substance ciclosporin. The ophthalmic emulsion is packaged at a 0.4 mL fill volume in 0.9 mL capacity low density polyethylene (LDPE) unit-dose vials.

The formulation was developed for topical ocular delivery. Due to the insolubility of ciclosporin in water, the chosen pharmaceutical form is oil in water emulsion. The pharmaceutical development work has been described in detail. The formulation composition of the early stage clinical drug product

batches was different than the final formulation, however all pivotal clinical trials used the final product formulation. Concerns raised over the presence of castor oil as an excipient have been allayed.

Actuation force data show that the force required to dispense a drop from the single dose container is within the capability of the target population, while drop size study data demonstrate reproducible dose delivery within the target drop size. Usability of the container is further confirmed by reference to pharmacovigilance data for commercial Restaysis product marketed in the USA.

Manufacture of the product and process controls

Name and address of the facility undertaking manufacture, batch release, testing and packaging are given. Satisfactory GMP status of the drug product manufacturer has been certified.

The manufacturing process is classified as a non-standard method since the emulsion is a specialised pharmaceutical dosage form and aseptic manufacturing (filling, mixing and form-fill-seal) are applied. It was found that terminal moist heat sterilisation had a detrimental effect on the quality of the product so sterile filtration and aseptic processing were considered justified. The proposed commercial process was adequately validation on 3 production scale batches of finished product.

However, CHMP requested that bioburden testing be introduced as an in-process control (IPC) prior to sterile filtration. This was not possible during the procedure so the applicant submitted a post-authorisation change management protocol (PACMP), giving details of how bioburden testing will be implemented post-authorisation. This included an acceptable protocol for re-validation of the process.

Control of excipients

The excipients used in the finished product comply with the Ph. Eur. monograph. The specification for carbomer copolymer Type A includes a test for viscosity. However, in view of the critical function of carbomer as a viscosity enhancing excipient and stabiliser for the emulsion, the applicant is requested to stipulate the manufacturer's grade used in manufacture of the clinical and validation batches. Furthermore, there is a concern that proposed limit for microbiological quality for purified water is too high in view of the expected bioburden limit of the part solutions; justification or tightening of the limits is requested All the other excipients are considered adequately controlled.

Control of drug product

The proposed finished product specification is generally acceptable to control product quality. The analytical methods have been adequately described and validated.

Container closure system

The drug product is filled into pharmaceutical grade LDPE single dose containers, which are formed using a form-fill-seal manufacturing process. The fill volume is 0.4 ml. Relevant properties of the container are monitored during the filling stage of manufacturing process; however, an additional visual inspection of the containers for sharp edges and plastic burrs around the dropper tip should be stipulated.

The LDPE plastic material comply with requirement of Ph. Eur. monograph 3.1.4 and suitability of the finished container including the labelling ink has been demonstrated by investigation of leachables in the drug product which show that levels of leachable impurities in the product are of no toxicological concern.

Stability

Stability data is provided for 12 commercial scale batches stored under long term and accelerated conditions. Photostability, freeze-thaw, and container leachable stability testing were also performed.

In-use stability data provided support the proposed in-use shelf-life of 30 days when product is stored in the original packaging to protect from light.

Microscopic images provided for various batches show that there is no change in the globule size distribution of the emulsion throughout the proposed shelf-life.

The proposed shelf-life of 24 months when the product is stored below 25 °C is accepted.

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, grant of a Marketing Authorisation may be recommended subject to presentation of a plan for implementation of the pre-sterilisation bioburden testing of the part solutions in a Post Approval Change Management Protocol, and resolution of the outstanding 'other concerns'.

3.2. Non clinical aspects

The toxicity profile of ciclosporin is well known following systemic administration and given that the proposed drug product is being marketed for optical use, no further systemic toxicology studies were conducted and are not required. The Applicant has conducted pivotal ocular toxicity studies in the rabbit and dog, supported by a summary of systemic toxicity studies available in the literature, which is acceptable.

3.2.1. Pharmacology

In primary pharmacodynamic studies, COE at concentrations up to 0.2% b.i.d. for 12 weeks were assessed in three ocular toxicity studies: in dogs with/without spontaneous chronic idiopathic keratoconjunctivitis sicca (KCS) and in a mouse model induction of desiccating stress (DS)-induced dry eye. In the dog, decreases in lymphocytic infiltrates in the conjunctiva and nictitans lacrimal gland, decreased inflammation, increased corneal transparency and improvement in the gross appearance of the ocular surface was suggestive that CsA (0.2%) can restore lacrimal gland and ocular surface functions in dry eye. Treatment at 0.05% ciclosporin did not show any histological improvement in the dog. However, mice exposed to desiccating stress (DS) and receiving COE 0.05% displayed reduced dry eye severity. DS mice receiving CD4+ T-cells from topical COE 0.05% had significantly less tear levels of TNF-α, as compared to DS mice treated with a placebo. Additional supportive evidence provided in response to questions raised at D120, was inconclusive regarding the effects of Restasis compared to vehicle, as measured with of CFS and goblet cell counts. However, CD4+ T-cell counts were substantially reduced compared to DS and DS+ vehicle groups. Collectively, these studies demonstrate the nonclinical in vivo pharmacological efficacy in dog and mouse model of DED demonstrating utility for treating human DED and other ocular inflammatory diseases. . Final interpretation of the clinical efficacy data is therefore required.

A discussion on the secondary pharmacodynamic, specific safety pharmacology and pharmacodynamic drug interactions of ciclosporin was not provided. However, the systemic exposure to ciclosporin following ocular administration of COE 0.05% is expected to be negligible and therefore the lack of secondary pharmacodynamic and specific safety pharmacology studies is considered acceptable. In terms of potential drug interactions, ciclosporin is known to interfere with the efflux transporters and is

an inhibitor of MRP1 and a wide range of drugs are known to interact with ciclosporin. As a result, the Applicant has amended section 4.2 of the SmPC to ensure that if more than one topical ophthalmic product is to be used, the different products should be instilled at least 15 minutes apart. This measure seems adequate considering the low perceived risk.

3.2.2. Pharmacokinetics

The pharmacokinetic profile of ciclosporin following systemic administration is well known. To support the MAA, the Applicant has conducted eight additional studies (six in rabbits; 2 in dogs) to investigate the ocular pharmacokinetics of ciclosporin.

Following intraocular administration of ciclosporin, high concentrations were detected in ocular surface tissues in both the rabbit and dog after single and repeated administration. Relatively low concentrations were detected in the internal ocular tissues in both species. Overall, ocular concentrations of ^{3}H-COE increased with dose following single and repeated administrations of ^{3}H-COE but tended to be less than dose proportional in both the surface and internal ocular tissues.

Distribution of ciclosporin in the eyes of rabbits and dogs supports the literature data on corneal concentrations and there is evidence of accumulation of the drug in some tissues of the eye. In addition, systemic exposure is considered to be very low in both the rabbit and dog following intraocular administration of ciclosporin for up to 12 months and up to six times daily. This suggests that there is poor systemic absorption of ciclosporin from the eye and therefore provides a low risk for systemic toxicity. However, long-term use of corticosteroids eye drops is associated with an increased risk of side effects such as cataracts and is noted that 3 cases of cataract occurred in the clinical trials (two with COE 0.1% and one with COE 0.05%). The negative findings with COE in the toxicology studies corroborate the position that COE treatment is unlikely to be associated with increased cataract risk.

The iris-ciliary body tissue concentrations of ciclosporin in both the rabbit and dog were comparable, with a tendency for lower exposure in the pigmented species, suggesting that ciclosporin does not bind to melanin. Furthermore, minimal penetration into the internal ocular tissues with very low exposures and minimal accumulation in the iris-ciliary body, choroid-retina and uveal tract, also indicate that melanin binding is unlikely to occur in patients.

Ciclosporin is not metabolised in rabbit or dog ocular tissues as no metabolites of ciclosporin were detected in rabbit conjunctiva, cornea, sclera, aqueous humour, iris-ciliary body, choroid-retina, or lacrimal gland, nor in the corneal and conjunctival tissues of dogs.

Elimination of ciclosporin from the eye is via a triphasic manner, with extensive half-lives in the external ocular tissues and a slow terminal phase. Elimination half-lives in NZW rabbits ranged from 25 to 57 hours and from 16 to 42 hours in dogs after single or multiple doses. The high concentrations and long elimination half-lives in the cornea indicate that the cornea is acting as a reservoir for ciclosporin, with slow release over a prolonged period. Accumulation of drug in tissues would therefore be expected following the proposed BID dosing. However, the corneal concentrations of ciclosporin after ophthalmic dosing of CsA 0.05% to human patients with various conditions requiring keratoplasty were approximately 40-50% of those in rabbits and are comparable to those in dogs. In addition, there was no evidence of ocular or systemic toxicity in the long-term tox studies dosed up to six times daily for 12 months. Therefore, the accumulation in the cornea is considered to have a low risk for clinical safety.

The SmPC of Restaysis states that "(…) No interaction of topically applied RESTAYSIS with systemic medicinal products is expected to occur." At the time when Restaysis was developed, circa 20 years

ago, very little was known about drug transporters in the eye. But now it is clear that many of them such as MDR1, MRP1-6 and breast cancer resistance protein (BCRP) are present and prostaglandin analogues, drugs widely used in glaucoma, are substrates of them. Based on the available evidence, the possibility of a drug-drug interaction at transporter level cannot be ruled out but the risk is considered to be low. The Applicant has proposed changes to the SmPC that seem to be an adequate measure and further action is not needed.

3.2.3. Toxicology

Single-dose ocular toxicity studies were not carried out or presented. In the light of repeat-dose ocular toxicity study data this omission is not of concern.

All pivotal in vivo nonclinical safety studies used the ocular route of administration as this is the intended route of clinical administration. Ocular toxicity studies with ciclosporin ophthalmic solution (COE) were conducted in rabbits for up to 6 months and in dogs for up to 52 weeks at concentrations up to 0.4% and administered up to 6x/day, with no signs of ocular or systemic toxicity or evidence of opportunistic ocular infections or systemic effects in these studies. Ocular discomfort and reddened conjunctiva (hyperaemia) were, however, consistent findings in both the rabbit and dog and occurred at all doses and in control animals. This was also reflected in findings from clinical studies where ocular burning was reported in patients, including those receiving vehicle, suggesting a local ocular tolerance issue related to the vehicle. One constituent of the vehicle, castor oil, has been shown to exert a cytotoxic effect on conjunctival cells, which could account for the tolerability issues observed. Further justification is required regarding the use of castor oil concentration in the vehicle. Based on the non-clinical and clinical data presented so far, it is inconclusive as to whether or not the proposed concentration of castor oil in the vehicle is leading to the local tolerance effects observed, including ocular burning. This point remains as part of an unresolved clinical major objection and will therefore not be progressed further.

The No-Observed Adverse Effect Level is therefore deemed to be 0.4% COE administered 6x/day, in both species giving an approximate 8.5- and 4-fold safety margin in the rabbit and dog, respectively, when compared to the single highest measured human concentration of 0.158 ng/mL.

In an extractable qualification study, no significant local tolerance or systemic toxicity was observed following ocular administration of 0.1% COE (with or without extractables) to rabbits six times daily for 1-month. Although two of the three remaining extractables have not been identified, they have been assessed in a previous toxicology study and are currently monitored as part of the stability testing. However, the container extractables and leachable studies, including the ink, should be provided for both proposed resins to confirm their suitability and the toxicological impact of leachables should be discussed taking into consideration the leachable levels observed at the end of the proposed shelf-life. This has been discussed in the Quality D150 Report and is therefore not pursued any further.

Based on literature evidence, no significant toxicity was observed at 6 and 5 mg/kg/day ciclosporin in the rat and monkey, respectively, following daily intravenous administration of ciclosporin for 4-weeks. At doses ≥24 mg/kg/day in rats and 25 mg/kg/day in monkeys, nephrotoxicity, hepatotoxicity, and lymphoid tissue atrophy and death occurred. Similar findings were also seen in a thirteen-week dietary study in the rat at 45 and 90 mg/kg/day ciclosporin, together with haematological and serum chemistry changes. There was no significant toxicity at 14 mg/kg/day. Following nasogastric intubation in the primate, decreases in white blood cell parameters, atrophic thymus changes, slight desquamation of tubular epithelium and dilated tubules in the kidneys, and moderate swelling and occasional hepatocyte necrosis was seen at 200 mg/kg/day ciclosporin A. There were no significant toxic effects at ≤ 60 mg/kg/day. In a 52-week oral gavage dog study, facial multilocular papilloma-like

lesions were recorded at 45 mg/kg/day ciclosporin A, which tended to regress spontaneously in some dogs. No malignant transformations were observed. Inconsistent reversible findings of marked anaemia, chronic periodontitis, gingivitis, lymphoid organ atrophy and slight regenerative changes in the tubular system of the kidneys were observed in all groups, including controls. The no toxic effect dose was 15 mg/kg/day, which provides an approximate 2000-fold safety margin compared to topical administration of COE 0.05%, twice daily in humans for up to 12 months. Given that the toxicity profile of Ciclosporin is well known following systemic administration, these findings are unlikely to translate into a clinical risk.

No additional genotoxicity, carcinogenicity or reproductive toxicity studies have been conducted. Literature evidence indicates that ciclosporin is not mutagenic or genotoxic. A potential for positive induction of sister chromatoid exchange occurred at concentrations ≥ 1 µg/mL *in vitro*, which represents a 6000-fold safety margin and therefore does not signify a significant clinical risk.

In a dietary carcinogenicity study in mice, ciclosporin-related hepatocellular carcinoma was seen at 16 mg/kg/day, together with virus-transformed lymphoblasts which may have resulted from ciclosporin immunosuppression. It could be argued that this is unlikely to occur following ocular topical administration due to the proposed low doses of ciclosporin that will be administered. However, given that Restaysis is intended to achieve local immunosuppressant action, there is a very low risk for peri-ocular skin malignancy and conjunctival and corneal neoplasia, which should be addressed in the RMP. This has been discussed in the D80 Clinical Report and is therefore not pursued further. The Applicant has amended the SmPC and Module 2.6.6 of the dossier to align the text with a lack of carcinogenicity findings in mice, and is now acceptable. There was no evidence of a carcinogenic effect in rats at exposures significantly in excess (approx. 1100-fold) of the single highest measured human concentration.

Ciclosporin did not impair fertility in male and female rats at oral doses up to 15 mg/kg/day and was not teratogenic in rats (up to 17 mg/kg/day) and rabbits (up to 30 mg/kg/day). Foeto- and embryotoxicity and postnatal effects were observed in rats and rabbits at doses that were maternally toxic (30 and 100 mg/kg/day, respectively). In a prenatal and postnatal development study in rats, ciclosporin was embryo- and foetotoxic at a maternally toxic dose (45 mg/kg/day) as indicated by increased pre- and postnatal mortality and reduced foetal weight together with related skeletal retardation. The foeto- and embryotoxicty observed has been adequately addressed in the product literature.

Ciclosporin does not pose a phototoxicity risk.

The proposed levels of impurities are in line with Ph.Eur (drug substance) or ICH guideline (ICH Q3B (R2) – drug product) and the excipients used in the final drug product are well characterised and correspond with the Pharm Eur.

3.2.4. Ecotoxicity / environmental risk assessment

The Log K_{ow} value quoted and calculated $PEC_{surfacewater}$ value suggest that ciclosporin is not a PBT compound and does not pose a risk to the environment. The Applicant has submitted a revised ERA, with the following results:

- The LogP value for ciclosporin was derived experimentally using the shake-flask method, which is acceptable. The derived LogP value of 4.34 is higher than that quoted in the original ERA (3.35) but is still below the threshold value of 4.5. Therefore, screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.

- The calculation of the $PEC_{surfacewater}$ and $DOSE_{ai}$ values in the revised ERA have used a droplet size of 28.6 µL/drop (or 114 µL of COE 0.05%/day), as requested. The revised values for $PEC_{surfacewater}$ and $DOSE_{ai}$ are 0.0020 µg/L and 0.057 mg/day ciclosporin, respectively.
- A refined market penetration (Fpen) of 7.06, which incorporates the exposure of ciclosporin in the environment form other medicinal products has been used to recalculate the $PEC_{surfacewater}$ value. Using the revised F_{pen}, the $PEC_{surfaceater}$ value = 0.002 µg/L, which is approximately 10-fold higher than the original calculation but is still below the threshold limit of 0.01 µg/L. Therefore a Phase II environmental fate and effect analysis is not required.

3.2.5. Discussion on non-clinical aspects

No Major Objections have been raised in the non-clinical context.

With regard to pharmacology, the applicant has conducted two studies in the spontaneous chronic KCS dog model that investigated the nonclinical efficacy of ciclosporin in dry eye. The data from these studies is supported by referenced data from studies conducted in mouse models of KCS and desiccating stress (DS)-induced DED. The studies in the dog showed that ciclosporin (0.2%) can restore lacrimal gland and ocular surface functions in dry eye. However, treatment of dogs with 0.05% CsA improved in clinical signs, like luster, but showed no histological improvement. The associated literature in the mouse model of DED, also indicated that topical delivery of COE 0.05% was efficacious in inhibiting the development of experimental dry eye disease. The mice in this study were exposed to desiccating shock for 5 days and evaluated for tear cytokines and immune cell infiltration. Additional supportive evidence was inconclusive regarding the effects of Restasis compared to vehicle, as measured with of CFS and goblet cell counts. However, CD4+ T-cell counts were substantially reduced compared to DS and DS+ vehicle groups.. The lack of a discussion on the secondary pharmacodynamic and specific safety pharmacology aspects of ciclosporin is deemed acceptable given the expected negligible exposure following ocular administration of COE 0.05% in patients. However, ciclosporin is known to interfere with the efflux transporters and is an inhibitor of MRP1 and a wide range of drugs are known to interact with ciclosporin. Appropriate measures have been taken in the SmPC.

The pharmacokinetic profile of Restaysis has been evaluated in both ocular and systemic in vivo studies in the NZW rabbit and beagle dog. High dose-related ocular surface tissues concentrations were detected in both the rabbit and dog after single and repeated ocular administration, which tended to be less than dose-proportional. Relatively low concentrations were detected in the internal ocular tissues and systemically in both species, suggesting that there is poor systemic absorption of CsA following ocular administration of COE and therefore a minimal risk for systemic toxicity. The negative findings with COE in the toxicology studies corroborate the position that COE treatment is unlikely to be associated with increased cataract risk. CsA is not metabolised in rabbit or dog ocular tissues and evidence of accumulation of the drug in some tissues of the eye was observed. The cornea is considered to be acting as a reservoir for CsA, with slow release over a prolonged period and therefore accumulation of drug in tissues would be expected following the proposed BID dosing. Elimination was via a triphasic manner, with extensive half-lives in the external ocular tissues and a slow terminal phase. The accumulation in the cornea is considered to have a low risk for clinical safety. However, given that many drug transporters are found in the eye (e.g. MDR1, MRP1-6 and BCRP). Based on the available evidence, the possibility of a drug-drug interaction at transporter level cannot be ruled out but the risk is considered to be low. The Applicant has proposed changes to the SmPC that seem to be an adequate measure and further action is not needed.

In general toxicity studies, ocular discomfort and reddened conjunctiva (hyperaemia) was observed in all groups, including controls, following topical ocular administration of COE up to 0.4% 6 times per day for up to 6 months in rabbits and 52 weeks in dogs. These findings suggest a local tolerance issue associated with the vehicle, which was also reflected in the clinical studies. One constituent of the vehicle, castor oil, has been shown to exert a cytotoxic effect on conjunctival cells, which may have explained the tolerability issues observed clinically and non-clinically. The Applicant was asked to address this. Concern in relation to the presence of castor oil has been sufficiently allayed – see clinical assessment. No other ocular or systemic toxicity and no opportunistic ocular infections or systemic effects were observed. In an extractable qualification study, no significant local tolerance or systemic toxicity was observed following ocular administration of 0.1% COE (with or without extractables). Although two of the three remaining extractables have not been identified, they have been assessed in a previous toxicology study and are currently monitored as part of the stability testing, which is acceptable.

Evidence from cited literature indicates that systemic exposure to significantly high doses of CsA leads to death, nephrotoxicity, hepatotoxicity, and lymphoid tissue atrophy in the rat and monkey, which are known toxicity findings associated with ciclosporin. In the dog, facial multilocular papilloma-like lesions were recorded at 45 mg/kg/day after 52-weeks of oral administration of ciclosporin. The no toxic effect dose was 15 mg/kg/day, which provides an approximate 2000-fold safety margin and therefore these findings are unlikely to translate into a clinical risk.

Literature evidence indicates that ciclosporin is not mutagenic or genotoxic. A potential for positive induction of sister chromatoid exchange occurred at concentrations $\geq$ 1 µg/mL in vitro, which represents a 6000-fold safety margin and therefore does not signify a significant clinical risk. Ciclosporin-related hepatocellular carcinoma was seen in a dietary carcinogenicity study in mice, together with virus-transformed lymphoblasts which may have resulted from ciclosporin immunosuppression. The risk for peri-ocular skin malignancy and conjunctival and corneal neoplasia has been addressed in the RMP. The SmPC and Module 2.6.6 of the dossier have been amended to address the discrepancy between the reported results of the relevant carcinogenicity study and the original short summary of this study in the chapter 5.3 of SmPC, and are now acceptable. There was no evidence of a carcinogenic effect in rats at exposures significantly in excess (approx. 1100-fold) of the single highest measured human concentration.

Although the proposed levels of impurities are in line with Ph.Eur (drug substance) or ICH guideline (ICH Q3B (R2) – drug product) and the excipients used in the final drug product are well characterised and correspond with the Pharm Eur, there was concern regarding the use of castor oil as an excipient in the final drug product. From a clinical perspective this is considered to have been satisfactorily addressed.

3.2.6. Conclusion on non-clinical aspects

There are no outstanding non-clinical issues.

3.3. Clinical aspects

3.3.1 Introduction

- **Tabular overview of main clinical studies**

Table 1:

Protocol Number/ Study Design	Treatment	N	Comparator	N	Randomized Treatment Duration	Key Inclusion Criteria	Key Efficacy Measures
Phase 2							
192371-001 Multicentre, investigator-masked, randomized, parallel group, vehicle controlled, dose-response United States	COE[a] 0.05% 0.1% 0.2% 0.4%	 31 32 34 32	Vehicle[b]	33	12 weeks	• Schirmer test (without anaesthesia) ≤ 7 mm/5 min in at least one eye; if 0 mm/5 min, then Schirmer with nasal stimulation ≥ 3 mm/5 min in at least one eye **AND** • corneal staining ≥ +1 in at least one eye **AND** • at least 1 subjective symptom of ocular discomfort (burning/stinging, tearing, discharge, itching, foreign body sensation, blurred vision, dryness, photophobia, soreness/pain) ≥ +2 (moderate) in at least one eye	**Objective:** Corneal and interpalpebral conjunctival staining, Schirmer tear test (without anaesthesia) **Subjective**: OSDI score, symptoms of dry eye
Phase 3/3b, 6-month masked, randomised, controlled							
192371-002 Multicentre double-masked randomized parallel group vehicle-controlled United States	COE 0.05% 0.1% Extension: COE 0.05% 0.1%	N 135 134 102 190 (100/90)[d]	Vehicle	N 136	6 months Extension: 6 months (total of 12 months exposure)	• Schirmer test (without anaesthesia) ≤ 5 mm/5 min in at least one eye; if 0 mm/5 min, then Schirmer with nasal stimulation ≥ 3 mm/5 min in the same eye **AND** • sum of corneal and interpalpebral conjunctival staining ≥ +5 in the same eye where corneal staining ≥ +2 **AND** • at least 9 responses on the OSDI questionnaire other than 'not applicable' (N/A) and responses were in a combination to achieve the minimum required entry score **AND** • Facial Expression Subjective Rating Scale ≥ 3	**Objective:** Corneal and interpalpebral conjunctival staining, Schirmer tear test (with and without anaesthesia) **Subjective**: OSDI score, symptoms of dry eye

Protocol Number/ Study Design	Treatment	N	Comparator	N	Randomized Treatment Duration	Key Inclusion Criteria	Key Efficacy Measures
192371-003 Multicentre double-masked randomized parallel group vehicle-controlled United States	COE 0.05% 0.1% Extension: COE 0.05% 0.1%	N 158 158 125 235 (114/121)[d]	Vehicle	N 156	6 months Extension: 6 months (total of 12 months exposure)	• Schirmer test (without anaesthesia) ≤5 mm/5 min in at least one eye; if 0 mm/5 min, then Schirmer with nasal stimulation ≥3 mm/5 min in the same eye **AND** • sum of corneal and interpalpebral conjunctival staining ≥+5 in the same eye where corneal staining ≥+2 **AND** • at least 9 responses on OSDI questionnaire other than N/A and responses were in a combination to achieve the minimum required entry score **AND** • Facial Expression Subjective Rating Scale ≥3.	**Objective:** Corneal and interpalpebral conjunctival staining, Schirmer tear test (with and without anaesthesia) **Subjective**: OSDI score, symptoms of dry eye
192371-501 Multicentre double-masked randomized parallel group vehicle-controlled Europe	COE 0.05% 0.1% Extension: COE 0.05% 0.1%	N 143 146[c] 115 220 (108/112)[d]	Vehicle	N 150	6 months Extension: 18 months (total of 24 months exposure)	• Schirmer test (without anaesthesia) ≤5 mm/5 min in at least one eye; if 0 mm/5 min, then Schirmer with nasal stimulation ≥3 mm/5 min in the same eye **AND** • sum of corneal and interpalpebral conjunctival staining ≥+5 in the same eye where corneal staining ≥+2 **AND** • at least 9 responses on OSDI questionnaire other than N/A and responses were in a combination to achieve the minimum required entry score **AND** • Facial Expression Subjective Rating Scale ≥3.	**Objective:** Corneal and interpalpebral conjunctival staining, Schirmer tear test (with and without anaesthesia) **Subjective**: OSDI score, symptoms of dry eye
192371-503 Multicentre investigator-masked randomized parallel group REFRESH-controlled Europe	COE 0.05%	N 124	REFRESH	N 119	6 months (planned; study was terminated early)	• Schirmer test (with anaesthesia) >0 but <10 mm/5 min in the worse eye **AND** • sum of corneal and interpalpebral conjunctival staining ≥+5 in the worse eye where corneal staining ≥+2 **AND** • at least 1 subjective symptom of ocular discomfort (burning/stinging, sensitivity to light, sandy or gritty feeling, itching, blurred vision, dryness, pain)	**Objective:** Corneal and interpalpebral conjunctival staining, Schirmer tear test (with anaesthesia) **Subjective**: OSDI score, symptoms of (eye) discomfort

3.3.2. Pharmacokinetics

Clinical studies have been conducted to evaluate the pharmacokinetics following topical administration. The extent of systemic exposure in humans was monitored in the Phase 2 dose-finding Study 192371-001 performed with 0.05%, 0.1%, 0.2%, and 0.4% CsA and in the Phase 3 efficacy and safety, performed with COE 0.05% and 0.1%. Additionally, the PK profile of CsA in human tears was monitored in the Phase 3 study. A publication describing the penetration of topical aqueous 0.5% CsA solution into the cornea and anterior chamber is also described.

No data are available on the elimination from the eye in humans but in monkeys the half-life is reported to be long (26- 44h) concentrations in human tears however show a short half-life and drug is not measurable post 3 hours. It is apparent that there are multiple phases to the elimination e.g. aqueous humour concentrations are stated to decrease in a triphasic manner with an initial half-life of 1.3 hours, and mid-phase half-life of 12 hours, and a slow terminal phase. High concentrations and long elimination half-lives in ocular surface tissues, especially the cornea, suggest that these tissues act as a reservoir for CsA, sequestering CsA and releasing it slowly over prolonged periods. Therefore the apparent elimination half-life in tears is probably limited by the sensitivity of the assay and only represents the initial elimination phase. In non-clinical studies in rabbits it is stated that there was a two- to eight-fold accumulation in most tissues following repeated dosing and accumulation in lens, vitreous humour, and optic nerve head was up to 37-fold, however concentrations in these tissues remained relatively low (below 70 ng-eq/g).

Blood concentrations of CsA are low; there are only 5 patients in the phase 2 dose escalation study, and 6 from the phase 3 studies, who have quantifiable plasma concentrations, this limits conclusions, however there is some evidence of higher exposure as the dose increases. At the proposed dose of 0.05% all the samples are below the limit of quantitation of 0.1 ng/ml and there is no significant accumulation in plasma with 6 months of dosing. This exposure in plasma is several orders of magnitude lower than that seen following dosing of oral products.

RESTAYSIS has not been studied in patients with renal or hepatic impairment, based on the low systemic availability. However, no dose adjustment or higher incidence of adverse drug reactions in patients with impaired renal or hepatic function would be expected. The study population was predominantly female and exposure data is limited, however there is not an obvious difference based on gender. There is also insufficient data to analyse the effect of race, weight, or age on systemic exposure, however there is some indication from the phase 3 study of higher exposure in older patients.

Owing to below quantifiable levels of CsA in systemic circulation no PK interaction studies are required.

3.3.3. Pharmacodynamics

The primary action of CsA is to inhibit the activation of T-lymphocytes and subsequent immune mediated inflammation. COE 0.05% is thought to interrupt the underlying immuno-modulated cytokine and receptor-mediated inflammatory process that leads to altered tear production in patients with DED. Regardless of initiating stimulus, immune-based inflammation is a central feature of DED pathology. Numerous studies have documented elevated lymphocytic activation markers (HLA-DR and ICAM-1), lymphocytes (CD3+, CD4+, CD8+) markers of apoptosis (Fas system and CD40 system) and cytokine secretion in DED patients compared to normal subjects. Reduced conjunctival goblet cell density has been reported as a common marker of the tissue damage resulting from the underlying inflammation.

Clinical studies have provided additional characterization of the immunomodulatory and anti-inflammatory actions of CsA. Conjunctival inflammation is reduced following CsA administration as quantified by a statistically significant reduction in the cellular expression of HLA-DR, lymphocytic markers (CD3, CD4, CD8), lymphocyte activation markers (CD11a) and other inflammatory markers such as CD40 ligand and Fas receptor. In addition, biopsies from DED patients treated with COE 0.05% for 6 months showed a significant decrease in IL-6 mRNA relative to pre-treatment biopsies. A reduction in these inflammatory biomarkers is representative of ocular surface healing. This is supported by data showing that DED patients treated with COE 0.05% demonstrate a statistically significant increase in conjunctival goblet cell expression. However, differences in biopsy site at baseline compared to post-treatment for goblet cell evaluation requires justification.

3.3.4. Discussion on clinical pharmacology

Ciclosporin (CsA) ophthalmic emulsion 0.05% (COE 0.05%) is an immunomodulator belonging to the therapeutic class of ophthalmologicals (S01XA18). The recommended dosage is one drop of RESTAYSIS instilled twice a day in each eye approximately 12 hours apart.

CsA is a cyclic undecapeptide immunomodulator, which acts to inhibit proliferation and activation of T-cell lymphocytes and subsequent immune mediated inflammation.

Ciclosporin exerts a range of anti-inflammatory and immunomodulatory effects with a number of potential markers of response.

Systemic absorption of CsA from the topically applied emulsion is very low and considered not clinically relevant. Blood concentrations are several orders of magnitude below those seen for oral formulations.

A local ocular permeation study has been conducted with aqueous 0.5% formulation but not the emulsion formulation. This revealed penetration of ciclosporin into the cornea and anterior chamber but has limited relevance as local penetration will be substantially influenced by the formulation. Non-clinical studies, including in primates, reveal high concentrations and long elimination half-lives in ocular surface tissues, especially the cornea, suggesting that these tissues act as a reservoir for CsA, sequestering CsA and releasing it slowly over prolonged periods.

Secondary pharmacodynamic and safety pharmacology studies are not considered necessary given the largely undetectable levels of ciclosporin in blood even after twice daily ocular administration for 12 months.

Although systemic drug-drug interaction studies are not required, efflux transporters are expressed on the ocular epithelium and therefore drug-drug interactions with other topically applied ophthalmic agents needs to be considered. Ciclosporin is known to inhibit efflux transporters including MRP1 and a wide range of drugs are known to interact with ciclosporin. As a result, the Applicant has amended section 4.2 of the SmPC to ensure that if more than one topical ophthalmic product is to be used, the different products should be instilled at least 15 minutes apart. This measure is considered adequate.

In exploratory biomarker analyses a portfolio of inflammatory biomarkers, including those specific to the eye such as goblet cell density, provide encouraging evidence of an anti-inflammatory effect.

3.3.5. Conclusions on clinical pharmacology

There are no major concerns in relation to clinical pharmacology.

3.3.6. Clinical efficacy

A total of 19 clinical studies have been conducted with COE. Of these, 7 were primarily DED efficacy studies and are listed below. The remaining studies focused on safety (192371-004, -005, -502) and health economics (192731-505).

The 7 clinical studies conducted to evaluate efficacy of COE in DED include:

- Phase II: study 192731-001 (prototype CsA formulation with different excipient concentrations compared to the final formulation)

- Phase III/IIIb: studies 192731-002, -003, -501, -503, -011, -008

The current application is primarily based on a retrospective analysis of a pooled subgroup of patients from the Phase III trials 192731-002, -003 and -501 conducted in the 1990's to investigate COE for the treatment of patients with moderate to severe DED. The re-analysis focuses on a subgroup of patients with moderate DED. The retrospective analysis was considered sufficient by the competent regulatory authority in Canada to support registration of COE 0.05% after a prior refusal of authorisation.

The Canadian EAG advised on the selection of the Level 2/3 DEWS population. It is accepted that this is a clinically identifiable target population within the DED spectrum. The Applicant had previously shared with the EAG an extensive breakdown of the data in this population compared with the overall ITT population.

3.3.6.1 Dose response

Phase II study 192371-001

This evaluated the safety, tolerability and efficacy of ciclosporin (0.05%, 0.1%, 0.2% and 0.4%) and vehicle ophthalmic emulsions in the treatment of moderate to severe keratoconjunctivitis sicca (KCS) The study was a multicentre, double-masked, randomised, parallel-group, dose response study. It consisted of a washout phase, 12 week treatment phase and a 4 week post-treatment follow-up. REFRESH tears were allowed as needed, but not more than eight times daily. Study medications were instilled twice daily to both eyes for 12 weeks.

Each concentration of the active drug had a different formulation to accommodate the solubility of CsA. The 0.2% CsA formulation, excluding CsA, was used as the vehicle control.

During the post-treatment phase, patients stopped study medication but continued to instill REFRESH as needed, but not more than eight times a day for four weeks.

Nine sites in the US enrolled 162 patients, 129 in the CsA group and 33 in vehicle. 92.6% completed. 2.5% discontinued due to adverse events.

COE 0.1% demonstrated a consistent trend to superior benefit over COE 0.05% in all objective evaluation outcomes (increase from baseline in Schirmer score; decrease from baseline in corneal fluorescein staining; decrease from baseline in conjunctival rose bengal staining) as well as in the OSDI index, a validated patient reported composite outcome measure that evaluates symptoms and visual function. 0.05% COE showed some evidence of efficacy in other patient response evaluations. There was no substantive or consistent improvement in efficacy – either objective or patient reported - with COE 0.2 and 0.4% compared with COE 0.1%. The selection of COE 0.05% and COE 0.1% for the Phase III studies is considered appropriate.

3.3.6.2 Main efficacy studies

The original analyses of the ITT populations in the respective pivotal Phase III clinical studies that contributed to the subsequent pooled subgroup analysis are considered first. These studies were retrospectively designated as pivotal.

3.3.6.2.1. Original analyses

Phase III Studies (192731-002, 192731-003, and 192731-501)

Studies 192731-002 and 192731-003 were conducted in the US and Study 192731-501 was conducted in Europe. These studies were identical vehicle-controlled studies with respect to patient population, duration of treatment phase for evaluation of primary and secondary efficacy (6 months), and key efficacy measures. Evaluation of systemic pharmacokinetic profile was conducted in Study192731-002. In each of these studies, various exploratory biological analyses characterizing mechanism of action and / or biological response were performed at selected sites.

All 3 pivotal Phase 3 studies shared the same objective and study design:

Objective: To evaluate the safety and efficacy of COE 0.05% and 0.1% compared to vehicle in patients with moderate to severe DED.

Study Design: Multicentre, double-masked, randomized, vehicle-controlled, parallel-group studies. Following a 2-week run-in phase, where patients instilled aqueous artificial tears [REFRESH; containing 1.4% polyvinyl alcohol and 0.6% povidone] daily as needed, patients were randomized to 1 of 3 treatment groups: COE 0.05%, 0.1%, or vehicle. Patients administered their randomized treatment into each eye twice daily for 6 months. REFRESH artificial tears could also be used daily as needed, but from Month 4 onwards, patients were asked to use REFRESH less than 8 times daily. Following the vehicle-controlled 6-month treatment phase, patients entered a 6-, 12-, or, 18-month extension phase, where patients who were randomized at baseline to either COE 0.05% or 0.1% continued on the same regimen, whereas all vehicle treated patients were switched to COE 0.1%.

Main criteria for inclusion:

Schirmer (without anaesthesia) ≤5 mm/5 min in at least one eye; if 0 mm/5 min, then Schirmer with nasal stimulation ≥3 mm/5 min in the same eye AND sum of corneal and interpalpebral conjunctival staining ≥ +5 in the same eye where corneal staining ≥+2 AND at least 9 responses on the Ocular Surface Disease Index (OSDI) questionnaire other than “N/A” and responses were in a combination to achieve the minimum required entry score AND Facial Expression Subjective Rating Scale ≥ 3

Efficacy measures:

In the -002, -003 and -501 study protocols the primary efficacy variables are specified as i) the Sum of corneal and interpalpebral conjunctival staining and ii) Ocular Surface Disease Index (OSDI) with secondary efficacy variables of Facial Expression Subjective Scale , Symptoms of dry eye, Schirmer tear test (with and without anesthesia), Tear break-up time and Global evaluation of response to treatment (investigator's evaluation).

Results: study -002

The main ITT efficacy results at month 6 are summarised below.				
Variable	0.05% ciclosporin	0.1% ciclosporin	Vehicle	P-value*
Mean change from baseline at month 6 (N)				
Corneal staining	-0.94 (129)**[a]	-0.73 (124)**	-0.51 (126)**	0.008
Sum of corneal and interpalpebral staining	-2.52 (129)**[a]	-2.13 (124)**	-1.77 (126)**	0.044
Categorised Schirmer values				
without anaesthesia	0.62 (135)**	0.69 (134)**	0.58 (136)**	0.612
with anaesthesia	0.41 (135)**	0.21 (133)	0.02 (136)	0.066
OSDI©	-0.11 (128)**	-0.11 (124)**	-0.06 (127)**	0.069
Facial Expression Subjective Rating	-0.69 (128)**	-0.85 (124)**[b]	-0.45 (127)**	0.044
Composite symptoms	-3.32 (128)**[a]	-4.03 (124)**[b]	-1.83 (127)**	0.008
Average daily REFRESH® use	-1.79 (126)**	-1.23 (124)**	-0.07 (127)	0.124
% responders at month 6 (n/N)				
OSDI© responder analysis	36/128 (28.1%)	47/124 (37.9%)[b]	30/127 (23.6%)	0.042
Global response	71.9% (92/128)[a]	71.0% (88/124)[b]	58.7% (74/126)	0.034
Responder analysis	50.0% (58/116)[a]	44.2% (50/113	31.2% (34/109)	0.014

Table footnote: ** Change from baseline to month 6 was statistically significant ($P \leq 0.014$). * P-value for among-group differences. [a] 0.05% ciclosporin and vehicle statistically significant different in pairwise comparison ($P \leq 0.035$). [b] 0.1% ciclosporin and vehicle statistically significant different in pairwise comparison ($P \leq 0.027$).

The overall results for mean change from baseline in a range of efficacy parameters were indicative of a vehicle effect. The sum of corneal and interpalpebral conjunctival staining showed nominal statistically significantly difference for 0.05% COE versus vehicle. Schirmer scores (increase in tear production) with anaesthetic were numerically better with 0.05% COE compared with vehicle. Patient reported outcome measures including OSDI responder analysis and composite symptoms, in addition to global response, favoured COE 0.1% (difference being nominally statistically significant from vehicle). Any clear evidence of incremental benefit for active treatment over vehicle at either COE 0.1% or COE 0.05% is not evident and the regulatory assessment conclusions from the original submissions can be understood.

From the efficacy results it is difficult to dismiss that these results did not influence the choice of the key efficacy parameters for the retrospective subgroup analysis.

It is noted from the CSR that subgroup analyses were performed in severe disease, per protocol population, Sjögrens patients (who comprised 27-29% of the ITT population by autoantibody analysis), age sex, race and iris colour. There were general similarities between the ITT analysis and the subgroup analyses.

Given that severe but not moderate DED was specified for a subgroup analysis this undermines that moderate DED was *a priori a* subgroup of interest.

The summary statistics presented above are not true to the intention-to-treat principle as the total numbers of patients for each endpoint are sometimes different to the total numbers of patients randomised and treated in each group.

Results: study -003

Efficacy Results continued: The main ITT efficacy results at month 6 are summarised below				
Variable at month 6	0.05% ciclosporin	0.1% ciclosporin	Vehicle	P-value*
Mean change from baseline (N):				
Sum of corneal and interpalpebral staining	-2.22 (152)	-2.17 (150)	-2.33 (146)	0.828
Corneal staining	-0.84 (153)	-0.93 (150)	-0.78 (147)	0.394
Categorised Schirmer values				
without anaesthesia	0.42 (158)	0.53 (158)	0.44 (156)	0.777
with anaesthesia	0.36 (155) [a]	0.31 (154) [a]	-0.18 (152)	<0.001
OSDI©	-0.08 (152)	-0.09 (149)	-0.09 (146)	0.876
Facial Expression Subjective Rating	-0.60 (152)	-0.59 (148)	-0.70 (145)	0.448
Composite symptoms	-2.53 (152)	-2.02 (149)	-2.44 (146)	0.859
Average daily REFRESH® use	-2.34 (150)	-1.51 (148)	-1.15 (142)	0.087
% responders (n/N):				
OSDI© responders	25.0% (38/152)	28.9% (43/149)	31.5% (46/146)	0.459
Global response	65.6% (99/151)	64.2% (95/148)	66.7% (98/147)	0.964
Responder analysis	42.6% (58/136) [a]	46.2 % (60/130) [a]	29.2% (38/130)	0.012
*Among group P-value				

Vehicle again demonstrated an effect which was greater than in study -002. The Schirmers test for COE versus vehicle looked encouraging in this study. Heterogeneity in outcomes between the studies is emerging.

As with study -002, a subgroup analysis in the severe patients was performed in which statistically significant among-group differences were found favouring ciclosporin over vehicle for corneal staining (-0.85 vs -0.49 for COE 0.1% vs vehicle at month 4, p=0.042; -0.92 vs -0.63 for COE 1% vs vehicle at month 6, p=0.047). This again undermines that the moderate DED patient subgroup was a priori a subgroup of particular interest which is one of the specified criteria in the CHMP guideline on subgroup analysis needed for justifying a subgroup analysis for registration purposes.

Results: study -501

Table of results of key efficacy variables in the ITT analysis								
Variable	**Mth**	**0.05% CsA**		**0.1% CsA**		**Vehicle**		**Between-Group[Ψ]**
Mean changes from baseline		**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	
Corneal staining:	1	128	-0.59***	133	-0.59***	136	-0.42***	0.05% vs Veh 0.029 0.1% vs Veh 0.042
	3	133	-0.65***	137	-0.69***	144	-0.45***	
	4	133	-0.80***	137	-0.78***	144	-0.50***	0.05% vs Veh 0.018 0.1% vs Veh 0.028
	6	136	-0.73***	139	-0.92***	145	-0.70***	
OSDI©	1	128	-0.05**	132	-0.06***	133	-0.04***	
	3	132	-0.07***	136	-0.07***	142	-0.07***	
	4	132	-0.09***	136	-0.09***	142	-0.07***	
	6	134	-0.11***	136	-0.10***	142	-0.09***	
Composite symptoms	1	128	-1.16**	132	-1.58***	134	-1.16***	
	3	132	-1.73***	136	-2.13***	142	-1.68***	
	4	132	-2.29***	136	-2.51***	142	-1.66***	
	6	134	-2.78***	136	-3.17***	142	-2.45***	
HLA DR:								
% positive cells	3	36	-26.67***	30	-15.47**	32	-5.09	0.05% vs Veh 0.006
	6	44	-23.00***	39	-22.23***	41	-6.68	0.05% vs Veh 0.034 0.1% vs Veh 0.028
Arbitrary units of fluorescence	3	35	-81240***	30	-46270	33	-13140	0.05% vs Veh 0.009 0.05% vs 0.1% 0.013
	6	44	-68635***	39	-111000***	42	-16387	0.05% vs Veh 0.022 0.1% vs Veh 0.011
Responders:		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
Corneal staining responders	1	68/128	53.1%	69/133	51.9%	59/136	43.4%	
	3	72/133	54.1%	73/137	53. 3%	62/144	43. 1%	
	4	76/133	57.1%	72/137	52.6%	61/144	42.4%	0.05% vs Veh 0.016
	6	73/136	53. 7%	87/139	62. 6%	79/145	54. 5%	
Overall disease severity index	3	39/99	39.4%	34/91	37.4%	24/101	23.8%	0.05% vs Veh 0.022 0.1% vs Veh 0.043
	6	46/123	37.4%	45/119	37.8%	41/126	32.5%	
Global response: moderate and above	1	23/128	18. 0%	31/132	23. 5%	30/136	22. 1%	
	3	49/133	36. 8%	42/136	30. 9%	34/144	23. 6%	
	4	50/133	37. 6%	52/136	38. 2%	42/144	29. 2%	
	6	66/137	48. 2%	60/138	43. 5%	58/144	40. 3%	
*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001: statistically significant within-group mean changes from baseline. [Ψ]Statistically significant between-group P-values								

Once again there was evidence of a vehicle effect with several of the outcome measures showing no clearly demonstrable benefit for ciclosporin over vehicle (including the Schirmer's test which is not included in the summary table). This contrasts with study -003 and again demonstrates heterogeneity in outcomes between the three studies. The Applicant draws attention to the greater reduction in cells expressing the inflammatory cell surface marker HLA-DR for ciclosporin versus vehicle (reaching nominal statistical significance). It is agreed that this is indicative of an anti-inflammatory effect of ciclosporin but there is no clear evidence of translation into clinical outcome.

3.3.6.2.2. Retrospective analysis of pooled subpopulation of patients with moderate DED from the Phase III studies 002, 003 and 501

Summary of main efficacy results

The following table and accompanying text summarises the efficacy results from the retrospective analysis of the pooled subpopulation of patients with moderate dry eye disease main supporting the present application. This should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2: Summary of efficacy for the pooled subpopulation re-analysis

Title: Re-Analysis of the Phase 3 Studies Evaluating the Efficacy of Cyclosporine 0.05% Ophthalmic Emulsion Used Twice Daily for 6 Months in the Treatment of Moderate to Moderately Severe Keratoconjunctivitis Sicca			
Study identifier	15 OCT 09 Re-analysis report		
Design	A retrospective analysis of a pooled subpopulation of moderate DED patients (DEWS Level 2/3) derived from three Phase III studies **192731-002, 192731-003, and 192731-501** that were similar in design. All were multicentre, double-masked, randomised, vehicle-controlled, parallel-group studies.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicable 6, 12 or 18 months
Hypothesis	Superiority		
Treatment groups	active		ciclosporin ophthalmic emulsion COE 0.05% 6 months, N=436
	vehicle		ophthalmic emulsion vehicle. 6 months, N=442
Endpoints and definitions	Co-Primary endpoint	Total staining responders	Total staining was calculated as the sum of corneal staining and conjunctival (interpalpebral temporal plus nasal). Total staining responders had a score of 0 at 6 months.
	Co-Primary endpoint	Blurred Vision Responders	A complete blurred vision responder was defined as a patient with blurred vision = 0 at the Month 6 evaluation.
	Secondary endpoint	Schirmer's test with anaesthesia responders	Responders were those who achieved an increase in Schirmer score, from baseline, of at least 10 mm in 5 min at month 6.

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Moderate DED – DEWS Level 2/3 - subpopulation) 6 months		
Descriptive statistics and estimate variability	Treatment group	COE 0.05%	Vehicle
	Number of subjects	142	160
	Total staining responders	12.0%	3.1%
	Blurred Vision Responders	49.6%	37.7%
	Schirmer's test with anaesthesia responders	17.1%	6.2%
Effect estimate per comparison	Co-Primary endpoint: Total staining	Comparison groups	COE 0.05% vs vehicle
		% Difference	8.8

	responders	95% CI	2.9, 14.8
		P-value	0.003
	Co-Primary endpoint: Blurred vision responders	Comparison groups	COE 0.05% vs vehicle
		% Difference	11.9
		95% CI	0.7, 23.1
		P-value	0.036
	Secondary endpoint: Schirmer test responders	Comparison groups	COE 0.05% vs vehicle
		% Difference	10.9%
		95% CI	3.3, 18.5
		P-value	0.005

Design, conduct and patient population

The re-analysis report submitted with the dossier summarises the results of retrospective analyses of data from phase III, multicentre, double-masked, randomised, parallel-group studies that had originally evaluated the efficacy of 0.05% and 0.1% ciclosporin ophthalmic emulsion, compared with vehicle, administered twice daily for 6 months in patients with moderate and severe keratoconjunctivitis sicca.

The Level 2-3 population was the primary analysis population and was comprised of the subset of the ITT population with all of the following baseline scores: corneal staining score of 2 – 4, total staining score of 5 – 9, Schirmer's with anaesthesia score > 2 mm/5 min, and blurred vision score ≤ 2.

The complement subgroup (Level 4) had at least one of the following at baseline: corneal staining > 4, total staining score >9, Schirmer score with anaesthesia < 2mm/5min, blurred vision score ≥ 3.

The allocation of patients into subgroups for the pooled retrospective analysis was performed in accordance with the DED severity classification drawn up by the International Dry Eye Disease Workshop in 2007 (b) where 4 degrees of severity are defined based on both symptoms and signs of DED. This classification system postdates the original pivotal studies. A retrospective evaluation of baseline disease severity of the patients in the original pivotal studies concluded that no patients were in DEWS Level 1 (mild) and all patients were at Level 2, 3 or 4, the majority of whom (57-78% across the pivotal studies) were in the severe category (level 4). The moderate DED subgroup was designated as patients in Levels 2 and 3 with Level 4 patients comprising the complement subgroup.

The Oxford scale (0-5) was used for the corneal and each of the interpalpebral (nasal and temporal) conjunctival staining scores which is a well recognised scale. Total staining scores were therefore on a possible scale of 0 – 15, 15 being maximum severity. The Applicant has justified the inclusion criteria for the Level 2/3 moderate DED subgroup, and the complement Level 4 subgroup. Overall the inclusion criteria are considered acceptable.

Although the DEWS classification criteria were applied retrospectively to identify Level 2 and Level 3 patients (moderate DED) it is acknowledged that moderate DED was a recognised clinical category of dry eye disease severity at the time the original trials were conducted (in the late 1990's). It is also acknowledged that a clinical driver of the retrospective analysis was the high unmet need in patients with moderate dry eye disease, in those patients insufficiently responsive to standard of care treatments which are largely artificial tears and lubricants. Ikervis (0.1% ciclosporin ophthalmic emulsion) is available for patients with severe keratitis. The consensus is that an unmet need is still present in patients with moderate dry eye disease, despite improvements in ocular lubricants.

In addition to clinical need, advancements in knowledge of disease aetiology have informed a new understanding that dry eye disease, regardless of the underlying trigger, develops into a cyclical immuno-inflammatory disease, which supports the rationale behind administering a topical immunosuppressant to disrupt T cell activation and its inflammatory consequences. Disruption of the immunoinflammatory cycle at an earlier – moderate – stage of the disease offers greater potential to prevent permanent inflammatory – fibrotic – changes in lacrimal glands and other associated structures, whilst allowing renewal of ocular surface epithelium to proceed. Evidence of repair of ocular surface epithelium, considered to be important, was sought in the assessment.

Concern remains however that the retrospective analysis may have been biased.

Primary efficacy variables

The primary analyses were for Month 6 evaluations of the ITT Level 2-3 population in the pooled key Studies -002, -003, and -501. Based on the recommendation of the External Advisory Group, there were 2 co-primary variables defined as follows.

• Total Staining Responders

The primary variable was the proportion of complete staining responders. Total staining was calculated as the sum of corneal staining and conjunctival (temporal plus nasal) A complete staining responder was defined as a patient with Total Staining = 0 at the Month 6 evaluation.

As an “intermediate assessment” for total staining response, additional responder analysis was conducted with a responder defined as a patient achieving at least a 3 point decrease in total staining score from baseline.

• Blurred Vision Responders

The primary variable was the proportion of blurred vision responders. A complete blurred vision responder was defined as a patient with blurred vision = 0 at the Month 6 evaluation. As patients did not require blurred vision for entry, a responder could include those patients whose blurred vision resolved or who had not developed blurred vision at Month 6.

Additional responder analyses was conducted for patients with blurred vision = 0 at baseline or blurred vision = 1 or 2 at baseline.

In evaluating a sign and a symptom of dry eye disease, the Applicant has taken note of clinical practice recommendations for evaluation of DED treatments. In exceptional circumstances where there is compelling evidence of objective evidence of improvement in ocular surface damage to the extent that it can be considered sight-preserving, evidence of symptomatic improvement may be less crucial.

The co-primary efficacy outcome measures selected are based on responder thresholds of complete response in ocular staining and blurred vision. It is agreed that these are stringent thresholds that represent a clinically relevant treatment benefit in an individual patient. It is also important however that a clinically relevant proportion of the patient population demonstrates a response. Furthermore, that non-responders demonstrate a trend to clinically relevant benefit that is supportive of response in the responder population.

The co-primary endpoints (statistically significant difference from vehicle) were both required to achieve significance at the two-sided 5% level and therefore no multiplicity correction was required. However, this assumes that the retrospective meta-analysis itself has been valid.

In the original meta-analysis the comparison between vehicle and ciclosporin was restricted to the 0.05% COE formulation, the 0.1% COE formulation having been prospectively excluded from the re-analysis even though the data were available from the original studies. At Day 120 CHMP requested provision of data for the 0.1% COE formulation.

Secondary efficacy variables

The key secondary efficacy variable was the proportion of Schirmer's with anaesthesia responders. A complete responder was defined as a patient with an increase from baseline ≥ 10 mm/5 min at Month 6 (Month 6 minus baseline).

Other efficacy assessments included corneal and conjunctival staining, the two components of total staining. A complete responder for each was defined as a patient with staining = 0 at the Month 6 evaluation.

The responder threshold for the Schirmer test identifies patients in whom tear production is restored to normal levels, given that a normal score in the Schirmer test is ≥ 10 mm/5 min. Again, this is acknowledged as a stringent, clinically relevant threshold but that must nonetheless be achieved by a clinically meaningful proportion of patients.

In addition to Month 6, evaluations of data over time (Months 1, 3, and 4 as applicable) were also performed for the primary, secondary and other efficacy variables.

As discussed earlier in the report, in the -002, -003 and -501 study protocols the primary efficacy variables are specified as i) the Sum of corneal and interpalpebral conjunctival staining and ii) Ocular Surface Disease Index (OSDI) with secondary efficacy variables of Facial Expression Subjective Scale , Symptoms of dry eye, Schirmer tear test (with and without anesthesia), Tear break-up time and Global evaluation of response to treatment (investigator's evaluation).

The efficacy variables chosen for the re-analysis differed from those in the original analyses in some important respects. For example, the Schirmer test was elevated to a key secondary efficacy variable for the retrospective pooled subgroup evaluation whereas other previously studied efficacy variables such as TBUT were downgraded in importance, despite tear break up time(TBUT) being regarded as an important indicator of improvement in tear quality and a meaningful readout of clinical improvement. Furthermore, only one (blurred vision) out of a possible twelve symptoms from the 3 domains in the OSDI composite score - ocular symptoms (sensitive, gritty, painful eyes, blurred/poor vision), vision-related everyday performance (reading/driving/computer/TV) and environmental triggers (discomfort in windy/dry/air conditioned atmosphere) – was selected as a co-primary efficacy variable for the pooled subgroup analysis. The downgrading of the overall OSDI composite score (from co-primary efficacy variable to a supportive efficacy variable only) was of particular concern given that this is a widely recognised and validated patient reported outcome of symptoms and their impact on everyday visual function which has been downgraded for no clearly provided reason. CHMP requested clearer justification for selective downgrading of key efficacy variables from key to supportive status, and vice versa.

Conclusions on endpoint selection

It is accepted that clinical need was a key motivator of the design of the retrospective analysis. It is hard to exclude however that the design of the retrospective analysis was data-driven in large part. Nonetheless, even if primarily data-driven, this does not immediately invalidate the results obtained from the retrospective analysis but there must be a very strong scientific and clinical rationale to explain the observed inconsistency between endpoints in the original pivotal studies. Endpoints that looked favourable in the original pivotal studies were upgraded for the retrospective analysis whereas

others were downgraded. It may be that these choices were data-driven or it may be that knowledge had advanced to support that these were valid choices. How these choices were arrived at originally (whether data-driven or informed by science) is less important than clarifying whether the choices have produced a non-biased outcome or whether they have unduly favoured the drug.

What is important here is not only providing scientific and clinical justification to support the endpoints that were upgraded but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the moderate dry eye patient population. The Applicant has concentrated in the responses thus far, largely on the former. What is needed now is an explicit view to support the clinical and scientific rationale for both upgrading and downgrading of endpoints. In the case of the latter, the downgrading of OSDI, previously assigned as a primary outcome measure, is a focus: why should moderate DED patients not be expected to obtain benefit on this endpoint, when one of the three domains concerns visual function and has 4 questions (reading, driving, computer, TV) when the Applicant asserts that everyday visual functioning is closely related to blurred vision, selected as the sole primary outcome. Also, TBUT and tear osmolarity were downgraded as endpoints. It is not immediately obvious why moderate DED patients would not demonstrate evidence of benefit on these endpoints with ciclosporin.

In the responses to the second list of issues the Applicant provides a reasonably cogent line of reasoning to support the selection of blurred vision as an important outcome measure. This seems to derive in part from expectation of improvement in corneal epithelium which will be important for central vision. The expert statement from Professor Rolando also supports that blurred vision is an important surrogate for tear film quality.

The Applicant is requested to provide a clear and robust justification to support not only why the endpoints that were upgraded would be expected (in the current state of knowledge) to demonstrate efficacy benefit in the proposed target population of moderate dry eye patients; but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the same population.

The following **Major Objection** is raised:

It should be clearly justified that the results across endpoints (favourable and unfavourable), trials, doses, patient populations are consistent with a hypothesis based on sound scientific rationale. There must be sufficient assurance that the design of the retrospective analysis has not biased the outcome in favour of the drug.

Statistical methods

Treatment group differences in responder rates were tested using the general association statistic of the Cochran-Mantel-Haenszel (CMH) test stratified by study. If statistically significant differences were detected at baseline, the analysis was performed stratifying by study and baseline. The appropriateness of pooling the studies for each primary and secondary endpoint was evaluated by testing the treatment-by-study interaction using the Breslow-Day test. A treatment difference was considered to be statistically significant if the p-value was ≤ 0.050. Tests of treatment-by-study interaction were considered to be statistically significant if the p value was < 0.100.

The statistical methods are appropriate but it should be noted that a non-significant treatment-by-study interaction could be a result of lack of power of the test rather than an absence of such an

interaction. The Applicant was asked to calculate I^2 for the primary and efficacy variables and discuss the extent of heterogeneity based on that. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance is an intuitive and simple expression of the inconsistency of studies' results.

Results from the re-analysis

Patient population and discontinuations:

In the pooled pivotal study ITT population 33.9% of patients in the COE 0.05% treatment group and 38 % of patients in the vehicle treatment group met the criteria for DEWS Level 2/3 (moderate). Median disease severity scores at baseline overall support lack of meaningful imbalance between treatment arms.

In the primary analysis population (moderate DED patients in the pooled pivotal studies 192731-002, -003, -501) patients had a median age of 60 years, 90% were Caucasian and 79% female. The demographic profile was similar to that in the overall ITT population.

Although non-Caucasian patients were in the minority, there is no known difference between racial groups in nature or severity of DED. Females were in the majority which is consistent with a higher incidence in females in older patients. Demographic characteristics were generally balanced between treatment arms apart from a higher percentage of men in the vehicle arm. Patients diagnosed as having Sjögren's syndrome from autoantibody testing, a population of interest, comprised 27-29% of the overall ITT population.

There were discontinuations in both treatment arms (Restaysis and vehicle) in the pooled pivotal studies 002 003 and 501 and ocular burning was the commonest reason for these. Adverse event data from the non-pivotal studies 008 and 503 (where REFRESH, twice daily, was the comparator arm) demonstrated a statistically significant difference between treatment arms in ocular adverse events and ocular burning. Cross-study comparison with Restaysis vehicle-controlled studies suggested a higher incidence of ocular burning with Restaysis vehicle, potentially implicating the vehicle and castor oil as an excipient. The comparison is not reliable however due to the possibility of bias towards under-reporting of adverse events in the REFRESH arms given the single blind design of these studies. Furthermore, concern over castor oil has been largely allayed following the submission of further non-clinical and clinical data.

Missing data:

Last observation carried forward (LOCF) was used to handle missing data. Sensitivity analyses including handling of missing data as failures have been provided. Sensitivity analyses support the original conclusions. Missing=failure analyses are reported in section 5.1 of the SmPC.

Outcomes:

Co-primary endpoints:

Total staining responders

Baseline mean total staining scores were similar in the COE 0.05% and vehicle groups (6.4 ± 1.27 versus 6.4 ± 1.28 respectively, p = 0.679) for the moderate subgroup from the 3 pooled pivotal studies (192371-002, -003, and -501).

In the moderate DED subgroup from the 3 pooled pivotal studies, a statistically significant greater proportion of patients in the COE 0.05% group were complete total staining responders compared to the vehicle group at Month 6 (12.0% vs 3.1% respectively, p = 0.003) (Table 3 below).

This result is supported by the results of each of the individual Phase 3 studies which showed numerical superiority of COE 0.05% over vehicle. In addition, results of the 5 pooled studies detected a statistically significant difference between the 2 treatment groups favouring COE 0.05% at Month 6.

In the complement subgroup of patients with severe DED, total staining responder rates were similar with COE 0.05% and vehicle. The responder analysis in the ITT population of the 3 pooled pivotal studies supported the results observed in moderate DED patients. Although lower percentages of responders were seen in the COE 0.05% treatment group compared with the moderate DED analyses, the advantage of COE 0.05% compared to vehicle was generally maintained.

Table 3: Complete Total Staining Responders: Proportion of Patients With a Score of 0 at Month 6

	Moderate DED			Severe DED			ITT		
Study(ies)	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]
Pooled Pivotal Studies (-002, -003 & -501)	12.0% (17/142)	3.1% (5/160)	**0.003** 8.8 (2.9, 14.8)	1.8% (5/272)	2.8% (7/254)	0.477 -0.9 (-3.5, 1.7)	5.3% (22/417)	2.9% (12/416)	0.088 2.4 (-0.3, 5.1)
-002	7.7% (4/52)	1.8% (1/57)	0.190[c] 5.9 (-2.1, 13.9)	1.3% (1/77)	2.9% (2/69)	0.603[c] -1.6 (-6.3, 3.1)	3.9% (5/129)	2.4% (3/126)	0.722[c] 1.5 (-2.8, 5.8)
-003	19.2% (10/52)	6.9% (4/58)	0.053 12.3 (-0.2, 24.9)	2.0% (2/98)	3.4% (3/87)	0.667[c] -1.4 (-6.2, 3.3)	7.9% (12/152)	4.8% (7/146)	0.274[c] 3.1 (-2.4, 8.6)
-501	7.9% (3/38)	0% 0/45	0.092[c] 7.9 (-0.7, 16.5)	2.1% (2/97)	2.0% (2/98)	>0.999[c] 0.0 (-4.0, 4.0)	3.7% (5/136)	1.4% (2/144)	0.271[c] 2.3 (-1.4, 6.0)
-503[d]	22.2% (6/27)	6.1% (2/33)	0.124[c] 16.2 (-1.5, 33.8)	1.4% (1/72)	5.6% (4/71)	0.209[c] -4.2 (-10.3, 1.8)	7.8% (8/102)	5.7% (6/106)	0.530[c] 2.2 (-4.6, 9.0)
-011[e]	3.3% (1/30)	0.0% (0/33)	0.476[c] 3.3 (-3.1, 9.8)	1.8% (2/114)	0.0% (0/108)	0.498[c] 1.8 (-0.7, 4.2)	2.1% (3/144)	0% (0/141)	0.247[c] 2.1 (-0.2, 4.4)
All 5 studies pooled	12.1% (24/199)	3.1% (7/226)	**<0.001** 9.0 (3.9, 14.0)	1.7% (8/458)	2.5% (11/433)	0.413 -0.8 (-2.7, 1.1)	5.0% (33/663)	2.7% (18/663)	**0.032** 2.3 (0.2, 4.3)

CI = confidence interval; COE = ciclosporin ophthalmic emulsion; DED = dry eye disease; Diff = difference; ITT = intent-to-treat population

[a] p-values are from the Cochran-Mantel-Haenzel test stratified by study for pooled analyses and the Chi Square test for individual studies.

[b] The 95% CI for the between-group difference in the responder rate is constructed using the normal approximation to the binary distribution.

[c] Fishers Exact test used: at least 25% of expected cell counts were less than 5.

[d] Study 192371-503 utilized REFRESH as the control.

[e] Study 192371-011 included a restricted patient population with more severe disease and worse prognosis.

Source: Module 5.3.5.3, Re-analysis Report, Attachment 1, Table 2-2.1 (moderate) and Table 2-5.1 (ITT), and Module 5.3.5.3, Efficacy Analyses Table 1.1 (severe)

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.003) in favour of COE 0.05% versus placebo in the percentage of complete staining responders at 6 months. This was in a minority of the population, however, (12.6%) with 8.9% of patients benefiting over vehicle alone. Nonetheless, given that this is a stringent measure of efficacy, reflecting complete resolution of punctate staining associated with ocular surface epithelial damage, in these patients this is a meaningful response. None of the individual studies demonstrated a significant difference but this is understandable as they were not powered for this analysis and the same trend to benefit for COE 0.05% over vehicle was demonstrated. The sample population size had to be increased by pooling to increase the power.

The same trend in favour of COE 0.05% for complete staining responders was seen in the individual studies as it also was in mean change from baseline in total staining (sum of corneal and interpalpebral temporal and nasal conjunctival staining) in the individual studies with a greater reduction in staining

in the COE 0.05% versus vehicle group in study -002 (-2.52 versus -2.13); and -2.22 versus -2.17 in study -003 ; and -0.73 versus -0.70 (corneal staining only) in study -501 . However, the incremental benefit for COE 0.05% over vehicle was very small (-0.05 to -0.39 in total staining) when one considers that the scale ranged from 0 to 15 (each of the 3 regions scored as 0 – 5) with the moderate DED subgroup patients required to have a baseline total staining score of 5-9. This casts doubt on clinical relevance in the subpopulation as a whole.

Severe DED population

The Applicant asserts that the subgroup analyses have revealed a lack of benefit in the severe DED (complement) group compared with the moderate DED group. It is agreed that there is no evidence of benefit for the COE 0.05% formulation (1.8% complete responders) over vehicle (2.8% complete responders) in the severe DED subgroup and the same trend is present in the individual studies. However, in the severe disease subgroup, it is understandable that few patients would achieve such a stringent threshold of response in a short time frame of 6 months, given that this is a high and unrealistic bar to aim for in this patient group. Although it is acknowledged that some severe patients may have a degree of ocular surface damage that is beyond hope of interrupting the injury-inflammation cycle, others may have capacity for clinically relevant improvement with topical immunosuppressant drugs and the clinical experience supports this. The choice of a stringent endpoint at a primary analysis time point of 6 months is unlikely to have had sufficient sensitivity to detect a response in this subgroup.

Patient accountability

There are some patients in the ITT population for each study who are classified neither as DEWS 2-3 nor DEWS 4. All ITT patients should be included in the analysis, with missing responses being classed as failures. This will result in larger denominators for the proportions and thus smaller response rates. The Applicant has provided sensitivity analyses using missing data as treatment failures and additional methods on ITT population. The sensitivity analyses on the co-primary efficacy endpoints on the pooled pivotal studies support the same conclusions as drawn in the original analyses: statistically significant results favouring COE 0.05% over vehicle.

Blurred vision responders

Baseline mean blurred vision scores were similar in the COE 0.05% and vehicle groups (1.1±0.85 vs 1.1±0.88 respectively, p = 0.868) for the moderate DED subgroup from the pivotal 3-study pool (192371-002, -003, -501). The percentages of patients with blurred vision scores at baseline of 2, 1, and 0 were 43.2%, 26.4%, and 30.4%, respectively, in the COE 0.05% group and 46.4%, 21.4%, and 32.1%, respectively, in the vehicle group.

A statistically significant greater proportion of patients in the moderate COE 0.05% group from the 3 pooled pivotal studies (192371-002, -003, -501), were complete blurred vision responders compared to the vehicle group at Month 6 (49.6% versus 37.7%, p = 0.036, Table 4, below). This result is supported by the results of each of the individual Phase 3 studies (with the exception of Study192371-002), which demonstrate that the proportion of patients in the COE 0.05% group that were complete blurred vision responders was numerically greater than that in the vehicle group at Month 6. The result for Study 192371-003 reached statistical significance (52.9% vs 27.6% for COE 0.05% vs vehicle groups respectively; p = 0.007).

In the complement subgroup of patients with severe DED, complete blurred vision responder rates were numerically in favour of vehicle. In the ITT population, complete blurred vision responders rates were similar with COE 0.05% and vehicle.

Table 4: Blurred Vision Responders: Proportion of Patients With a Score of 0 at Month 6

Study(ies)	Moderate DED			Severe DED			ITT		
	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]
Pooled Pivotal Studies (-002, -003 & -501)	49.6% (70/141)	37.7% (60/159)	**0.036** 11.9 (0.7, 23.1)	22.7% (61/269)	28.2% (71/252)	0.181 -5.5 (-13.0, 2.0)	32.2% (133/413)	32.0% (132/413)	0.875 0.2 (-6.1, 6.6)
-002	38.5% (20/52)	40.4% (23/57)	0.840 -1.9 (-20.2, 16.5)	15.8% (12/76)	17.1% (12/70)	0.826 -1.4 (-13.4, 10.7)	25.0% (32/128)	27.6% (35/127)	0.642 -2.6 (-13.4, 8.2)
-003	52.9% (27/51)	27.6% (16/58)	**0.007** 25.4 (7.5, 43.2)	19.2% (19/99)	24.4% (21/86)	0.389 -5.2 (-17.2, 6.7)	30.9% (47/152)	25.5% (37/145)	0.301 5.4 (-4.8, 15.6)
-501	60.5% (23/38)	47.7% (21/44)	0.246 12.8 (-8.6, 34.2)	31.9% (30/94)	39.6% (38/96)	0.270 -7.7 (-21.3, 5.9)	40.6% (54/133)	42.6% (60/141)	0.743 -2.0 (-13.6, 9.7)
-503[c]	69.2% (18/26)	66.7% (22/33)	0.834 2.6 (-21.4, 26.5)	46.5% (33/71)	46.5% (33/71)	>0.999 0.0 (-16.4, 16.4)	52.5% (52/99)	51.9% (55/106)	0.927 0.6 (-13.0, 14.3)
-011[d]	69.2% (10/29)	51.5% (17/33)	0.177 -17.0 (-41.3, 7.3)	21.9% (25/114)	22.4% (24/107)	0.929 -0.5 (-11.5, 10.5)	24.5% (35/143)	29.3% (41/140)	0.361 -4.8 (-15.1, 5.5)
All 5 studies pooled	50% (98/196)	44.0% (99/225)	0.182 6.0 (-3.5, 15.5)	26.2% (119/454)	29.8% (128/430)	0.295 -3.6 (-9.5, 2.4)	33.6% (220/655)	34.6% (228/659)	0.809 -1.0 (-6.1, 4.1)

CI = confidence interval; COE = ciclosporin ophthalmic emulsion; DED = dry eye disease; Diff = difference; ITT = intent-to-treat population

[a] p-values are from the Cochran-Mantel-Haenzel test stratified by study for pooled analyses and the Chi Square test for individual studies.

[b] The 95% CI for the between-group difference in the responder rate is constructed using the normal approximation to the binary distribution.

[c] Study 192371-503 utilized REFRESH as the control.

[d] Study 192371-011 included a restricted patient population with more severe disease and worse prognosis.

Source: Module 5.3.5.3, Re-analysis Report, Attachment 1, Table 3-2.1 (moderate) and Table 3-4.1 (ITT), Module 5.3.5.3, Efficacy Analyses, Table 1.6 (severe)

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.036) in favour of COE 0.05% versus placebo in the percentage of complete blurred vision responders at 6 months. This occurred in 49.6% of patients with COE 0.05% but was also demonstrated in 37.7% of patients in the vehicle group, 11.9% of patients benefiting from COE. The result was driven primarily by one of the studies (-003) in which 52.9% of patients in the COE 0.05% group versus 27.6% in the vehicle group demonstrated a complete response whereas in study -002 there was a numerical difference in favour of vehicle (40.4% versus 38.5%) indicating heterogeneity of response in this outcome measure between studies.

Given that blurred vision was not a requirement for study entry some patients had a score of 0 at study entry. The additional responder analyses in patients with (score 1 or 2) and without (0) blurred vision at baseline, as well as change from baseline in blurred vision score in these subgroups will be of interest. This is considered under ancillary analyses.

There is concern that only one (blurred vision) out of a possible twelve symptoms from the 3 domains in the OSDI composite score - ocular symptoms, vision-related everyday performance and environmental triggers – was selected as a co-primary efficacy variable for the pooled subgroup analysis.

Secondary efficacy endpoint:

Schirmer Test With Anaesthesia responders

At baseline, mean Schirmer test with anaesthesia scores were similar in the COE 0.05% and vehicle groups (6.2 mm/5 minutes and 6.5 mm/5 minutes, respectively, p = 0.494) for the moderate DED subgroup from the 3 pooled pivotal studies (192371-002, -003, and -501.

A statistically significant greater proportion of patients in the COE 0.05% group were complete Schirmer test with anaesthesia responders compared to the vehicle group at Month 6 (17.1% versus

6.2%, p = 0.005, Table 10, below) in the moderate DED subgroup from the 3 pooled pivotal studies. This result is supported by the results of each of the individual Phase 3 studies, which demonstrate that the proportion of patients in the COE 0.05% moderate DED subgroup that were complete Schirmer test with anaesthesia responders was greater compared to the vehicle group at Month 6. The result for Study 192371-003 reached statistical significance (17.0% vs 1.8% for COE 0.05% vs vehicle groups respectively; p = 0.011).

In the complement subgroup of patients with severe DED as well as in the ITT population, the treatment difference for complete Schirmer test with anaesthesia responder rates was also statistically significant, in favour of COE 0.05%, however, the magnitude of the difference was not as pronounced as in the moderate DED subgroup.

Table 5: Complete Schirmer Test With Anaesthesia Responders: Proportion of Patients With an Increase From Baseline ≥ 10 mm / 5 Minutes at Month 6

	Moderate DED			Severe DED			ITT		
Study(ies)	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]	COE 0.05% % (n/N)	Vehicle % (n/N)	P Value[a] Diff (95% CIs)[b]
Pooled Pivotal Studies (-002, -003 & -501)	17.1% (22/129)	6.2% (9/146)	**0.005** 10.9 (3.3, 18.5)	8.8% (22/251)	4.0% (9/225)	**0.038** 4.8 (0.4, 9.1)	11.5% (44/381)	5.1% (19/372)	**0.002** 6.4 (2.5, 10.4)
-002	25.0% (12/48)	13.7% (7/51)	0.155[c] 11.3 (-4.2, 26.7)	11.6% (8/69)	6.9% (4/58)	0.367 4.7 (-5.3, 14.7)	17.1% (20/117)	10.1% (11.109)	0.126 7.0 (-1.9, 15.9)
-003	17.0% (8/47)	1.8% (1/55)	**0.011**[c] 15.2 (3.9, 26.5)	8.9% (8/90)	1.3% (1/79)	**0.038**[c] 7.6 (1.2, 14.0)	11.7% (16/137)	1.5% (2/134)	**<0.001** 10.2 (4.4, 15.9)
-501	5.9% (2/34)	2.5% (1/40)	0.591[c] 3.4 (-5.9, 12.7)	6.5% (6/92)	4.5% (4/88)	0.747[c] 2.0 (-4.7, 8.6)	6.3% (8/127)	4.7% (6/129)	0.562 1.6 (-3.9, 7.2)
-503[d]	20.0% (5/25)	3.0% (1/33)	0.075[c] 17.0 (0.2, 33.7)	7.2% (5/69)	10.6% (7/66)	0.493[c] -3.4 (-13.0, 6.3)	11.3% (11/97)	7.9% (8/101)	0.414 3.4 (-4.8, 11.6)
-011[e]	16.7% (5/30)	9.1% (3/33)	0.462[c] 7.6 (-9.0, 24.1)	2.6% (3/114)	3.7% (4/107)	0.715[c] -1.1 (-5.7, 3.5)	5.6% (8/144)	5.0% (7/140)	0.834 0.6 (-4.6, 5.8)
All 5 studies pooled	17.4% (32/184)	6.1% (13/212)	**<0.001** 11.3 (4.9, 17.6)	6.9% (30/434)	5.0% (20/398)	0.262 1.9 (-1.3, 5.1)	10.1% (63/622)	5.5% (34/613)	**0.003** 4.6 (1.6, 7.6)

CI = confidence interval; COE = ciclosporin ophthalmic emulsion, DED = dry eye disease; Diff = difference; ITT = intent-to-treat population

[a] p-values are from the Cochran-Mantel-Haenzel test stratified by study for pooled analyses and the Chi Square test for individual studies.

[b] The 95% CI for the between-group difference in the responder rate is constructed using the normal approximation to the binary distribution.

[c] Fishers Exact test used: at least 25% of expected cell counts were less than 5.

[d] Study 192371-503 utilized REFRESH as the control.

[e] Study 192371-011 included a restricted patient population with more severe disease and worse prognosis.

Source: Module 5.3.5.3, Re-analysis Report, Attachment 1, Table 4-1.1 (moderate) and Table 4-3 (ITT), and Module 5.3.5.3, Efficacy Analyses Table 1.13 (severe)

The responder threshold which required an increase of at least 10 mm from baseline, for the Schirmer test is in principle clinically meaningful. However, there are a number of concerns over the analysis. Patients were recruited who had Schirmer's with anaesthesia score > 2 mm/5 min but there was no upper limit so patients with normal (≥ 10mm in 5 minutes) or close to normal tear production may have been enrolled which is also suggested by the mean baseline scores of ~ 6 mm/5 min in both subgroups.

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.005) in favour of COE 0.05% (17.1%) versus placebo (6.2%) in the percentage of Schirmer responders at 6 months. There was heterogeneity in the proportion of responders across the individual studies, although the same trend for benefit of COE 0.05% over vehicle was present in all (25 % versus 13.7 % in study -002; 17 % versus 1.8% in study -003; and 5.9% versus 2.9% in study -501).

Change from baseline data – primary efficacy and key secondary efficacy variables:

There was a small treatment difference between COE and vehicle for all the main efficacy outcomes, indicating only a small proportion of the population were gaining clear benefit from ciclosporin. Change from baseline data evaluation was requested, to inform response in the subgroup populations as a whole.

Moderate DED:

Ocular staining

In the moderate DED subgroup there was a very small treatment difference, in favour of COE 0.05%, in change from baseline total staining score at 6 months (-0.398, 95% CI -0.95, 0.15; p = 0.154). There was a not dissimilar numerical treatment difference for COE 0.05% versus vehicle in the severe DED subgroup (-0.286, 95% CI -0.69, 0.11; p = 0.160). These differences cannot be considered clinically relevant.

For the moderate DED subgroup when ocular staining is evaluated, the low responder rate and small overall change from baseline data indicates heterogeneity within the patient population, with a subset more clearly responsive to 0.05% COE but little evidence of benefit in the remaining patients.

Blurred vision

The moderate DED subgroup data for change from baseline blurred vision also does not support a clinically relevant treatment effect for the subgroup as a whole (treatment difference COE 0.05% versus vehicle, -0.141, 95% CI -0.41, 0.13, p = 0.308), again indicating heterogeneity within the population, with a more responsive subset.

Schirmer score

In the moderate DED subgroup the treatment difference for COE 0.05% is 2.667 mm, 95% CI 1.08, 4.26, p = 0.001, which suggests clinically relevant improvement in tear production in the moderate DED subgroup as a whole. There is a similar benefit with COE 0.1%. Improvement in tear production will be followed by a reduction in tear osmolarity. This supports a trend to a clinically relevant effect in the moderate DED subgroup overall but is not supported by staining or blurred vision outcomes.

Severe DED:

Ocular staining

In severe DED there was consistency between lack of treatment effect for ocular staining in the responder and change from baseline analyses, suggesting a uniformly non-responsive population.

Blurred vision

Unlike the responder analysis, in severe DED there was a nominally significant treatment difference for change from baseline in blurred vision score for COE 0.05% (and with COE 0.1%): for COE 0.05% versus vehicle a treatment difference of -0.246, 95% CI -0.46, -0.03; p = 0.026. This could be explained by a greater sensitivity of the severe DED population to revelation of improvement in blurred vision, given that more patients in the moderate DED subgroup had a blurred vision score of 0 at baseline (were already non-responders) compared with those in the severe DED subgroup. Without accompanying evidence of benefit on ocular staining this cannot be considered sufficient to support benefit of COE 0.05% in the severe DED subgroup.

Schirmer

Patients in the severe DED subgroup fail to demonstrate benefit on tear production with no evidence of a treatment effect for COE 0.05% (or COE 0.1%) on change from baseline tear production by Schirmer score: COE 0.05% vs vehicle, treatment difference 0.712 mm, 95% CI -0.16, 1.58, p = 0.108. This contrasts with the trend to improved tear production in the overall moderate DED patients. The lack of response in severe DED may be understood given a greater likelihood of permanent inflammation-induced fibrotic change in the lacrimal glands in more severe patients which will limit the extent of any improvement in tear production.

Conclusion from comparison of responder and change from baseline data:

In the severe DED subgroup the consistency in lack of treatment effect demonstrated by responder rate and change from baseline analyses, for total staining and Schirmer score, suggests a uniformly non-responsive population. There is heterogeneity of outcome however in the trend to improvement in blurred vision in the overall population. The data as a whole point to Restaysis (COE 0.05% and 0.1%) not being entirely ineffective in severe DED patients but the benefit is insufficient to support an indication in this subgroup.

Whereas, the moderate DED patient population seems to have a more clearly responsive subset, from the responder analyses, and with a trend to clinically relevant improvement in tear production in the overall moderate DED population.

Ancillary analyses

1) **Responder analysis of an intermediate staining response**

As an “intermediate assessment” for total staining response, an additional responder analysis was conducted with a responder defined as a patient achieving at least a 3 point decrease in total staining score from baseline. A greater percentage of patients in the ciclosporin 0.05% group achieved at least a 3-unit decrease in total staining score compared to the vehicle group at Month 6 in the 3-study analysis (50.7% vs. 41.9%), although the difference was not statistically significant (p = 0.127).

It is acknowledged that a 3 point decline in total (corneal and conjunctival) staining score over a period of 6 months can be considered a clinically relevant response in an individual patient where baseline staining score at study entry was in the range 5-9 in the moderate DED group. As expected, more patients do respond when evaluated by this less stringent threshold (50.7% in the COE 0.05% group) but so do patients in the vehicle group (41.9%) with a similar incremental benefit for ciclosporin over vehicle (8.8%) as was observed with the more stringent threshold of response. The less stringent responder threshold, still clinically meaningful, has not revealed a further benefit for ciclosporin over vehicle. Also, there was once more, heterogeneity of response between the individual studies.

This additional analysis has not provided reassurance of clinical relevance for the primary responder analysis outcome.

2) **Additional responder analysis of blurred vision in patients with baseline blurred vision score = 0 at baseline compared with those with blurred vision score of 1 or 2**

The blurred vision criterion for the moderate DED subgroup was a baseline score of 0, 1 or 2 (0- no blurring of vision; 4 = maximum blurring). Thus, for patients with a baseline blurred vision score = 0, a patient was considered to be a responder at Month 6 if the score remained 0. Patients with blurred vision scores of 1 or 2 were classified as responders if they no longer had this symptom at Month 6.

Responder analyses of these respective subgroups were carried out.

Moderate DED

In the pooled moderate DED population, in the subgroup without blurred vision at baseline, a higher percentage of patients remained without blurred vision in the COE 0.05% group (69.8%) compared with the vehicle group (58%) which was not statistically significant. Approximately one-third of patients in both treatment arms had no blurred vision at baseline. There was heterogeneity between studies with study -002 showing the opposite trend compared to studies -003 and -501. However, the patient numbers were small

In patients with blurred vision at baseline, numerically more patients lost this symptom in the COE 0.05% group than the vehicle group (40.8% versus 28.4%; p = 0.067). Again there was lack of consistency between the individual studies with -002 showing the opposite trend. Inclusion of patients without blurred vision at baseline does not appear to have affected the outcome of the primary blurred vision responder analysis.

Severe DED

In the pooled subpopulation analysis of severe patients the trend was in favour of vehicle (71.2 % versus 58.5% in those without blurred vision at baseline and 27.6% versus 25.2 in those moderate blurred vision). The data do not allow any inferences to be made about relative response in the moderate DED and severe DED groups as only ~ 55% of patients in the severe DED category had a baseline blurred vision score of 0,1 or 2 (the remainder presumptively having higher scores) whereas 100% of those in the moderate DED category did so (as one would expect from the inclusion criteria for the Level 2-3 population). Therefore these analyses did not capture the entire severe DED subgroup.

3) Ocular surface disease index (OSDI)

The OSDI questionnaire is an instrument developed by the Sponsor's Outcomes Research Group, and is a global assessment tool consisting of 12 questions designed to assess the symptoms of ocular irritation consistent with dry eye disease and their impact on vision related function. The questions cover three areas: ocular symptoms, ocular sensitivity to environmental insult, and vision-related function (the effect of eye problems on the ability to perform routine tasks).

Patients graded each of the 12 items of the OSDI questionnaire on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score was then calculated as were subscale scores. At the time of the original analyses of the Phase III/IIIb studies, the patient-reported grades were transformed to a scale of 0 (no disability) to 1 (complete disability). For the re-analyses of OSDI data, these grades were transformed to a scale of 0 to 100, with higher scores representing greater disability, as this is the current scale now used in practice. Subscale scores are computed similarly with only the questions from each subscale used to generate its own score.

The OSDI is a recognised patient-reported composite score of ocular discomfort and vision-related function. It was designated in the study protocols for the original pivotal studies as a primary efficacy variable but was downgraded to a supportive outcome in the re-analysis. Blurred vision is one of the 12 possible parameters. This was selected as a co-primary efficacy variable for the re-analysis.

Mean reductions from baseline in OSDI were -8.0±17.19 and -9.0±19.05 for COE 0.05% and vehicle respectively. The minimum clinically important difference for reduction in OSDI in patients with mild to moderate DED is reported to be 4.5-7.3 (where moderate DED has a score in the range 23-32).

Therefore, although the mean change suggests a clinically relevant difference, the SD was large indicating wide variation and deterioration in some patients also. There was no meaningful difference between COE 0.05% and vehicle.

Symptoms of discomfort

Symptoms of Discomfort were evaluated for Blurred Vision (designated as a co-primary endpoint), Dryness, Sandy or Gritty Feeling, Pain, Itching, Sensitivity to Light, and Burning/Stinging. Similar to Blurred Vision, for each of the symptoms, a responder was defined as a patient with a score of 0 at Month 6.

It is notable that except for sensitivity to light, the responder rate for all other symptoms of ocular discomfort was in favour of vehicle over COE 0.05%. The blurred vision responder rate, selected as a co-primary endpoint for the re-analysis, was by contrast in favour of COE. The selection of this endpoint, and the downgrading of the OSDI score, raises the question that the selection was informed by prior knowledge of symptom response in the other domains.

The Applicant presents a combined responder analysis at 6 months of patients who were both complete blurred vision responders and had other symptoms of discomfort that did not worsen which was in favour of COE 0.05% over vehicle for all symptoms of discomfort including burning (44.3% versus 32.1%)(Table 48 in summary of clinical efficacy in the dossier). However, this does not reveal the proportion of patients in whom ocular burning did worsen. The Applicant is asked to provide more details of ocular burning – patients in whom this worsened and to what extent - given that this is reported as a very common adverse event. Information at time intervals up to 6 months would also be helpful if available.

4) Tear film break up time (TBUT)

Tear film break up time is one of the DEWS severity classification parameters and is a measure of the quality of tears. TBUT is ≤ 10 secs in Level 2 disease and ≤ 5 secs in Level 3 disease (with immediate break up in severe disease).

Table 7

	Moderate DED			Severe DED			ITT Overall		
TBUT[a]	COE 0.05% Mean ± SD	Vehicle Mean ± SD	P Value[b] Diff (95% CI)	COE 0.05% Mean ± SD	Vehicle Mean ± SD	P Value[b] Diff (95% CI)	COE 0.05% Mean ± SD	Vehicle Mean ± SD	P Value[b] Diff (95% CI)
Baseline Mean (SD)	4.4±2.82 (n=147)	4.2±2.68 (n=165)	0.397 0.258 (-0.3, 0.9)	3.7±2.57 (n=280)	3.7±2.42 (n=269)	0.956 0.012 (-0.4, 0.4)	4.0±2.70 (n=431)	3.9±2.54 (n=437)	0.628 0.086 (-0.3, 0.4)
Month 6 Mean (SD)	4.3±2.65 (n=130)	4.1±2.56 (n=149)	0.448 0.233 (-0.4, 0.8)	3.8±2.43 (n=255)	3.8±2.33 (n=233)	0.985 0.004 (-0.4, 0.4)	4.0±2.51 (n=388)	3.9±2.44 (n=384)	0.739 0.059 (-0.3, 0.4)
Mean Change From Baseline at Month 6 (SD)	-0.1±2.93 (n=130)	-0.1±2.68 (n=146)	0.937 0.027 (-0.6, 0.7)	0.1±2.65 (n=252)	0.1±2.43 (n=232)	0.919 0.024 (-0.4, 0.5)	0.0±2.74 (n=385)	-0.0±2.52 (n=380)	0.863 0.033 (-0.3, 0.4)

COE = ciclosporin ophthalmic emulsion; CI = confidence interval; DED = dry eye disease; Diff = difference; SD = standard deviation; TBUT = tear-film break-up time

[a] TBUT was only measured in Studies 192371-002, -003, and -501.

[b] P-values for pooled data are from the 2-way analysis of variance (ANOVA), including treatment group and study as the main effects in the model. For individual studies, a one-way ANOVA was used.

Source: Module 5.3.5.3, Efficacy Analyses Tables 5.10.1 (moderate), 5.10.2 (severe), 5.10.3 (ITT)

An improvement in tear quality would be anticipated to lengthen the time taken for tear film breakup. There was no evidence of prolongation of TBUT with either COE 0.05% or vehicle. The downgrading of this efficacy endpoint for the retrospective analysis further raises the question that the results of the original analyses were used to inform the prioritisation of endpoints for the retrospective subpopulation analysis.

5) Tear osmolality

Table 8

Parameter Time	COE 0.05%	Vehicle	p-value[a]
Baseline (Day 0)			
N	16	17	
Mean ±SD	338.6 ± 24.4	339.4 ± 17.9	
Month 6			
N	9	14	
Mean change from baseline ±SD	342.8 ± 17.1	330.4 ± 21.1	p = 0.398

COE = ciclosporin ophthalmic emulsion; KCS = keratoconjunctivitis sicca; SD = standard deviation

[a] Among-group p-value from analysis of variance.

Module 5.3.5.4, Tear Osmolality Study 192371-003 (page 5)

A reduction in tear osmolality, consistent with improved tear production, might have been expected to follow the improvement in Schirmer's score. There was no change however in either treatment arm from baseline to 6 months.

There was no difference in TBUT between COE and vehicle at 6 months.

6) Shift analyses

Shift analyses were conducted on total staining, blurred vision and Schirmer test to evaluate incremental improvements according to baseline scores. The shift analyses for staining and blurred vision indicate a vehicle effect with a small incremental benefit for COE over vehicle in the less severe patients at baseline. In patients with scores bordering on severe, there was greater benefit for vehicle over COE but the patient numbers were small. Blurred vision worsened more often in the more severe patients with COE 0.05% versus vehicle.

These analyses therefore do not provide evidence of a trend except in the less severely affected moderate DED patients there is a vehicle effect and a small incremental benefit for patients receiving ciclosporin in staining and blurred vision. This does not discount an effect in more severely affected patients however as a longer time window than 6 months may be needed to demonstrate benefit.

7) Change in DEWS DED Severity Classification

As a means of differentiating overall treatment effect, analyses were conducted to determine if patients "shifted" in DEWS classification level from baseline in the 3 pooled pivotal studies (192371-002, -003, and -501).

The shift from L2/3 to Level 1 resembles that seen with the less stringent staining responder analysis in demonstrating a vehicle effect and a small incremental benefit with COE (an additional 10.5% of patients showing benefit with ciclosporin). This seems to be a consistent message: an additional ~ 10% of patients achieving clinically relevant benefit with COE 0.05% compared with vehicle. The question is whether this outweighs the risks. It is still premature to dismiss benefit in the severe DED patients even for the 0.05% formulation as the 6 month analysis window may have been too short to adequately investigate benefit in more severely affected patients where a greater degree of ocular epithelial damage may take longer to repair.

3.3.6.3. Clinical studies in special populations

No studies in renal or hepatic impairment were conducted which is considered acceptable given the low systemic absorption. The Applicant is requested to provide the numbers of subjects in the re-analysis in the age bands 65-74, 75-84 and 85+ yrs.

Children under the age of 18 were excluded from the clinical studies. The indication is appropriately restricted to the adult population. Section 4.2 *Paediatric population* in the SmPC should be re-worded to reflect lack of relevance to children. At present the wording suggests an omission in the absence of paediatric data.

3.3.7. Discussion on clinical efficacy

Dose finding:

A Phase II study evaluated the safety, tolerability and efficacy of ciclosporin (0.05%, 0.1%, 0.2% and 0.4%) and vehicle ophthalmic emulsions in the treatment of moderate to severe keratoconjunctivitis sicca (KCS).

COE 0.1% demonstrated a consistent trend to superior benefit compared with COE 0.05% in all objective evaluation outcomes (increase from baseline in Schirmer score; decrease from baseline in corneal fluorescein staining; decrease from baseline in conjunctival rose bengal staining) as well as in the OSDI index, a validated patient reported composite outcome measure that evaluates symptoms and visual function. 0.05% COE showed some evidence of efficacy in other patient response evaluations. There was no substantive or consistent improvement in efficacy – either objective or patient reported - with COE 0.2 and 0.4% compared with COE 0.1%. The selection of COE 0.05% and COE 0.1% for further evaluation in the Phase III studies was appropriate.

Original analyses: Phase III Studies (192731-002, 192731-003, and 192731-501)

Design and conduct

The studies 002,-003 and -501shared the same objective to evaluate the efficacy and safety of COE 0.05% and COE 0.1% compared to vehicle in patients with moderate to severe DED. The majority of patients had severe disease (57% -78% across the three studies, retrospectively classified as DEWS Level 4, a classification scheme that was not available at the time).

All three studies were multicentre, double-masked, randomised, vehicle-controlled, parallel-group studies in which patients were randomised to COE 0.05%, 0.1%, or vehicle. Following the vehicle-controlled 6-month treatment phase, patients entered a 6-, 12-, or, 18-month extension phase where all patients received active treatment.

In the original study protocols, the primary efficacy variables are specified as i) the Sum of corneal and interpalpebral conjunctival staining and ii) Ocular Surface Disease Index (OSDI), a validated patient reported composite score of symptoms related to ocular discomfort and vision-related function. Secondary efficacy variables of Facial Expression Subjective Scale, Symptoms of dry eye, Schirmer tear test (with and without anaesthesia), Tear break-up time and Global evaluation of response to treatment (investigator's evaluation).

The pre-specified variables in the original protocol are different from those presented in Table 1 (above) which designates the Schirmer test as a key variable but this appears to have been a retrospective assignation. There is no description of hierarchical evaluation to support this. This is important as Schirmer test was elevated to a key secondary efficacy variable for the retrospective

pooled subgroup evaluation whereas other previously studied efficacy variables such as TBUT were downgraded in importance. Furthermore, only one (blurred vision) out of a possible twelve symptoms from the 3 domains in the OSDI composite score - ocular symptoms (sensitive, gritty, painful eyes, blurred/poor vision), vision-related everyday performance (reading/driving/computer/TV) and environmental triggers (discomfort in windy/dry/air conditioned atmosphere) – was selected as a co-primary efficacy variable for the pooled subgroup analysis.

In the original analyses, efficacy was evaluated at intervals up to 6 months with no specification of 6 months as the primary analysis time point. 6 months is the time point chosen retrospectively for the pooled subgroup analysis. Statistical significance, if achieved, can only be viewed as nominal.

The statistical methods used for the original analyses were consistent with those of an exploratory analysis with descriptive statistics and no control of type I error for testing two doses against vehicle, or for multiple efficacy variables.

Individual study efficacy results

All three studies showed clear evidence of a vehicle effect but no clearly demonstrable benefit for ciclosporin over vehicle at either formulation strength. Where a numerical benefit was observed in a particular efficacy outcome, this was not replicated across the studies. The efficacy outcome where benefit was most consistently in favour of COE 0.05% compared with vehicle was total ocular staining. A pre-specified subpopulation analysis in severe patients in study -003 showed benefit for COE 0.1% over vehicle in ocular staining score but this was not recapitulated in other studies.

Retrospective analysis of a pooled subpopulation of patients with moderate DED (DEWS Level 2/3) pooled from studies 192371-002,-003 and -501

Design and conduct

A report is submitted of a retrospective analysis of the efficacy of ciclosporin 0.05% ophthalmic emulsion in a pooled subpopulation of patients classified as having moderate DED (DEWS Level 2-3) within the overall patient population in Phase III studies -002, -003 and -501 conducted in the 1990's (study initiation 1997).

The original Phase III studies were multicentre, double-masked, randomised, parallel-group studies evaluating the efficacy of ciclosporin 0.05% and 0.1% ciclosporin ophthalmic emulsion, compared with vehicle, given twice daily for 6 months in patients with moderate and severe keratoconjunctivitis sicca. The retrospective analysis was restricted to a comparison of vehicle with the 0.05% ciclosporin formulation strength with patients considered to have moderate DED (DEWS Level 2-3) as the primary analysis population.

The ITT Level 2-3 population was retrospectively defined based on the Dry Eye Workshop (DEWS) classification scheme and recommendations from a Canadian External Advisory Group. The DEWS classification scheme was not in existence at the time of the original studies. The Level 2-3 population was the primary analysis population with Level 4 patients the complement subgroup (no patients were classed as Level 1 – mild).

Although the DEWS classification criteria were applied retrospectively to identify Level 2 and Level 3 patients (moderate DED) it is acknowledged that moderate DED was a recognised clinical category of dry eye disease severity at the time the original trials were conducted (in the late 1990's). It is also acknowledged that a clinical driver of the retrospective analysis was the high unmet need in patients with moderate dry eye disease, in those patients insufficiently responsive to standard of care

treatments which are largely artificial tears and lubricants. Ikervis (0.1% ciclosporin ophthalmic emulsion) is available for patients with severe keratitis. The consensus is that an unmet need is still present in patients with moderate dry eye disease, despite improvements in ocular lubricants.

In addition to clinical need, advances in knowledge of disease aetiology have informed a new understanding that dry eye disease, regardless of the underlying trigger, develops into a cyclical immuno-inflammatory disease, which supports the rationale behind administering a topical immunosuppressant to disrupt T cell activation and its inflammatory consequences. Disruption of the immunoinflammatory cycle at an earlier – moderate – stage of the disease offers greater potential to prevent permanent inflammatory – fibrotic – changes in lacrimal glands and other associated structures, whilst allowing renewal of ocular surface epithelium to proceed. Evidence of repair of ocular surface epithelium, considered to be important, was sought in the assessment.

Patients in the pivotal vehicle-controlled studies were allowed liberal concomitant artificial tears – REFRESH – throughout (limited to 8 times per day beyond 8 weeks). Although there are more artificial tear options in current clinical practice, the pivotal study populations are considered on balance to be sufficiently reflective of patients with a need for an adjunct to tears or lubricants which matches the scope of the indication. The therapeutic indication has been revised to specify patients with moderate dry eye disease …who are inadequately responsive to artificial tears or ocular lubricants. The term moderate is somewhat helpful as a broad descriptor of severity but on its own too imprecise. The positioning of Restaysis after artificial tears or lubricants is considered more informative for the clinician.

Endpoint selection

Two co- primary efficacy endpoints were selected: Complete Ocular Staining responders to reflect a sign and Complete Blurred Vision responders to reflect a symptom. It is agreed that these are stringent thresholds of response that represent clinically relevant treatment benefit in an individual patient.

The key secondary efficacy variable was Schirmer responder rate whereby responders exhibit a minimum increase from baseline in tear production of 10 mm/5min which brings all responders into the normal range. Again this is acknowledged as a stringent outcome measure.

Treatment group differences in responder rates were tested using the general association statistic of the Cochran-Mantel-Haenszel (CMH) test stratified by study. If statistically significant differences were detected at baseline, the analysis was performed stratifying by study and baseline. The statistical methods are overall considered appropriate. Appropriate sensitivity analyses have been provided and support the original conclusions. The I^2 statistic was requested to evaluate heterogeneity.

There is concern that the efficacy variables chosen for the re-analysis are different from those used in the original analyses in some important respects. For example, the Schirmer test was elevated to a key secondary efficacy variable for the retrospective pooled subgroup evaluation whereas other previously efficacy variables were downgraded in importance. Of particular concern, only one (blurred vision) out of a possible twelve symptoms from the 3 domains in the OSDI composite score was selected as a co-primary efficacy variable for the pooled subgroup analysis. The ocular discomfort parameters were all downgraded.

It is accepted that clinical need was a key motivator of the design of the retrospective analysis. It is hard to exclude however that the design of the retrospective analysis was data-driven in large part. Nonetheless, even if primarily data-driven, this does not immediately invalidate the results obtained from the retrospective analysis but there must be a very strong scientific and clinical rationale to explain the observed inconsistency between endpoints in the original pivotal studies. Endpoints that

looked favourable in the original pivotal studies were upgraded for the retrospective analysis whereas others were downgraded. It may be that these choices were data-driven or it may be that knowledge had advanced to support that these were valid choices. How these choices were arrived at originally (whether data-driven or informed by science) is less important than clarifying whether the choices have produced a non-biased outcome or whether they have unduly favoured the drug.

What is important here is not only providing scientific and clinical justification to support the endpoints that were upgraded but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the moderate dry eye patient population. The Applicant has concentrated in the responses thus far, largely on the former. What is needed now is an explicit view to support the clinical and scientific rationale for both upgrading and downgrading of endpoints. In the case of the latter, the downgrading of OSDI, previously assigned as a primary outcome measure, is a focus: why should moderate DED patients not be expected to obtain benefit on this endpoint, when one of the three domains concerns visual function and has 4 questions (reading, driving, computer, TV) when the Applicant asserts that everyday visual functioning is closely related to blurred vision, selected as the sole primary outcome. Also, TBUT and tear osmolarity were downgraded as endpoints. It is not immediately obvious why moderate DED patients would not demonstrate evidence of benefit on these endpoints with ciclosporin.

In the responses to the second list of issues the Applicant provides a reasonably cogent line of reasoning to support the selection of blurred vision as an important outcome measure. This seems to derive in part from expectation of improvement in corneal epithelium which will be important for central vision. The expert statement from Professor Rolando also supports that blurred vision is an important surrogate for tear film quality.

The Applicant is requested to provide a clear and robust justification to support not only why the endpoints that were upgraded would be expected (in the current state of knowledge) to demonstrate efficacy benefit in the proposed target population of moderate dry eye patients; but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the same population.

The following **Major Objection** is raised:

It should be clearly justified that the results across endpoints (favourable and unfavourable), trials, doses, patient populations are consistent with a hypothesis based on sound scientific rationale. There must be sufficient assurance that the design of the retrospective analysis has not biased the outcome in favour of the drug.

Results of the re-analysis

Responder analyses:

Total ocular staining responders

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference ($p = 0.003$) in favour of COE 0.05% versus placebo in the percentage of complete staining responders at 6 months. This was in a minority of the population (12.6%) with 8.9% of patients benefiting over vehicle alone.

Blurred vision responders

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.036) in favour of COE 0.05% versus placebo in the percentage of complete blurred vision responders at 6 months. 49.6% of patients treated with COE 0.05% were complete responders but 37.7% of patients in the vehicle group were complete responders also; therefore an additional ~11.9% of patients only, benefited from the presence of COE. The result was driven primarily by one of the studies (-003) in which 52.9% of patients in the COE 0.05% group versus 27.6% in the vehicle group demonstrated a complete response whereas in study -002 there was a numerical difference in favour of vehicle (40.4% versus 38.5%) indicating heterogeneity of response in this outcome measure between studies.

Schirmer responders

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.005) in favour of COE 0.05% (17.1%) versus placebo (6.2%) in the percentage of Schirmer responders at 6 months. There was heterogeneity in the proportion of responders across the individual studies, although the same trend for benefit of COE 0.05% over vehicle was present in all (25 % versus 13.7 % in study -002; 17 % versus 1.8% in study -003; and 5.9% versus 2.9% in study -501).

Change from baseline:

Change from baseline data was requested, to inform response in the subgroup populations as a whole.

Moderate DED:

Ocular staining

In the moderate DED subgroup there was a very small treatment difference, in favour of COE 0.05%, in change from baseline total staining score at 6 months (-0.398, 95% CI -0.95, 0.15; p = 0.154). There was a not dissimilar numerical treatment difference for COE 0.05% versus vehicle in the severe DED subgroup (-0.286, 95% CI -0.69, 0.11; p = 0.160). These differences cannot be considered clinically relevant.

For the moderate DED subgroup when ocular staining is evaluated, the low responder rate and small overall change from baseline data indicates heterogeneity within the patient population, with a subset more clearly responsive to 0.05% COE but little evidence of benefit in the remaining patients.

Blurred vision

The moderate DED subgroup data for change from baseline blurred vision also does not support a clinically relevant treatment effect for the subgroup as a whole (treatment difference COE 0.05% versus vehicle, -0.141, 95% CI -0.41, 0.13, p = 0.308), again indicating heterogeneity within the population, with a more responsive subset.

Schirmer score

In the moderate DED subgroup the treatment difference for COE 0.05% is 2.667 mm, 95% CI 1.08, 4.26, p = 0.001, which suggests clinically relevant improvement in tear production in the moderate DED subgroup as a whole. There is a similar benefit with COE 0.1%. Improvement in tear production will be followed by a reduction in tear osmolarity. This supports a trend to a clinically relevant effect in the moderate DED subgroup overall but is not supported by staining or blurred vision outcomes.

Severe DED:

Ocular staining

In severe DED there was consistency between lack of treatment effect for ocular staining in the responder and change from baseline analyses, suggesting a uniformly non-responsive population.

Blurred vision

Unlike the responder analysis, in severe DED there was a nominally significant treatment difference for change from baseline in blurred vision score for COE 0.05% (and with COE 0.1%): for COE 0.05% versus vehicle a treatment difference of -0.246, 95% CI -0.46, -0.03; p = 0.026. This could be explained by a greater sensitivity of the severe DED population to revelation of improvement in blurred vision, given that more patients in the moderate DED subgroup had a blurred vision score of 0 at baseline (were already non-responders) compared with those in the severe DED subgroup. Without accompanying evidence of benefit on ocular staining this cannot be considered sufficient to support benefit of COE 0.05% in the severe DED subgroup.

Schirmer

Patients in the severe DED subgroup fail to demonstrate benefit on tear production with no evidence of a treatment effect for COE 0.05% (or COE 0.1%) on change from baseline tear production by Schirmer score: COE 0.05% vs vehicle, treatment difference 0.712 mm, 95% CI -0.16, 1.58, p = 0.108. This contrasts with the trend to improved tear production in the overall moderate DED patients. The lack of response in severe DED may be understood given a greater likelihood of permanent inflammation-induced fibrotic change in the lacrimal glands in more severe patients which will limit the extent of any improvement in tear production.

Conclusion from comparison of responder and change from baseline data:

In the severe DED subgroup the consistency in lack of treatment effect demonstrated by responder rate and change from baseline analyses, for total staining and Schirmer score, suggests a uniformly non-responsive population. There is heterogeneity of outcome however in the trend to improvement in blurred vision in the overall population. The data as a whole point to Restaysis (COE 0.05% and 0.1%) not being entirely ineffective in severe DED patients but the benefit is insufficient to support an indication in this subgroup.

Whereas, the moderate DED patient population seems to have a more clearly responsive subset, from the responder analyses, and with a trend to clinically relevant improvement in tear production in the overall moderate DED population.

Patients with Sjögrens syndrome as a population of interest

A breakdown of data in Sjögrens and non-Sjögrens patients was requested. In moderate DED, the treatment difference between COE 0.05% and vehicle for complete responder rate in total ocular staining was greater in Sjögren's syndrome patients (17.1%), and reached nominal statistical significance. Whereas in the overall population the responder rate difference was only 8.8%. There was also a 14.9% difference between COE 0.05% and vehicle in blurred vision complete responder rate, compared with a treatment difference of 11.9% in the overall population.

A bigger effect in Sjögrens patients can be understood from a clinical and scientific perspective and supports that ciclosporin is mediating an immunosuppressant action to reduce ocular surface damage. In patients with Sjögrens syndrome the initiating stimulus will be at least in part immune-mediated and is likely to amplify the subsequent cycle of immuno-inflammation.

The treatment difference in the Schirmer's complete responder analysis (normalisation of tear production) was less however in Sjögrens (7.5%) compared with non-Sjögren's patients (10.2%) or the overall population (11.9%). This might be expected given that in patients with Sjögren's syndrome there is more likely to be permanent (inflammation-induced fibrosis and immune-mediated) damage to lacrimal glands. Therefore there is less potential for normalisation of tear production in response to ciclosporin. However, Sjögren's patients will also be susceptible to inflammatory damage to the ocular surface epithelium resulting from inflammatory cytokines released by activated T cells, amenable to ciclosporin-mediated immunosuppressant action and ocular surface repair. Sjögrens patients nonetheless showed a treatment effect of up to 15% when partial Schirmer response was evaluated and is consistent with some improvement in tear production in these patients.

The evidence pointing to a more pronounced efficacy benefit (in both ocular staining and blurred vision) in Sjögren's syndrome patients is accepted and is considered to be in favour of ciclosporin's mechanism of action. The lack of incremental benefit on tear production can be understood and does not undermine the overall efficacy evaluation.

The indication presently specifies patients "including those with Sjögren's disease" which is not in line with CHMP's policy on the wording of the indication. Nonetheless, inclusion of data in Sjögren's patients in section 5.1 is considered informative for the clinician. The phrase "including Sjögrens disease" should be removed from the indication and should be replaced by a cross reference to section 5.1 at the end of the indication statement, in parenthesis "(See section 5.1)

Conclusions on clinical efficacy

There continues to be substantive concern that the retrospective analysis may have been biased in favour of the study drug. Other concerns are considered to have been sufficiently resolved that the benefit-risk could be considered positive if the outstanding major concern in relation to bias can be resolved. This will require the Applicant to put forward a very clear rationale to support the upgrading and downgrading of endpoints for the retrospective analysis and that the heterogeneity between outcomes, trials, patient populations and dose response can also be explained by sound scientific and clinical rationale. **A Major Objection is outstanding.**

3.3.8. Clinical safety

1.3.8.1. Introduction

Ciclosporin is a well-known immunosuppressant. Systemic CsA concentrations are largely undetectable following twice daily instillation of COE 0.05% for up to 12 months. Systemic immunosuppression is therefore unlikely.

Whereas systemic immunosuppression is unlikely, the potential for adverse events due to local ocular immunosuppression needs to be fully considered.

Safety data were pooled from studies -002,-003 and -501and comprised the overall ITT population of moderate and severe patients.

3.3.8.2. Patient exposure

Table 9

Exposure		Number (%) of Patients COE 0.05% (N = 1174) [a]
At least 1 day		1149 (97.9%)
At least 28 days	(4 weeks)	1102 (93.9%)
At least 84 days	(12 weeks)	1000 (85.2%)
At least 168 days	(24 weeks)	858 (73.1%)
At least 252 days	(36 weeks)	579 (49.3%)
At least 336 days	(48 weeks)	480 (40.9%)
At least 504 days	(72 weeks)	132 (11.2%)
At least 840 days	(120 weeks)	88 (7.5%)
At least 1008 days	(144 weeks)	52 (4.4%)

COE = ciclosporin ophthalmic emulsion

[a] 25 patients enrolled in the studies had incomplete data for the calculation of treatment exposure and are excluded from the totals

Source: Module 5.3.5.3, ASA, Table 2.7.4.1

There is sufficient patient exposure for a sufficient duration to support long term administration.

3.3.8.3. Adverse events

Adverse Events Irrespective of Causality, 192371-002, -003 and -501 Month 12 Pooled Data

In the pooled analysis of safety (studies 192371-002, -003 and -501), AEs irrespective of causality were reported for 281 (64.4%) and 299 (68.4%) patients in the COE 0.05% and COE 0.1% groups, respectively, during the 12-month study; 260 (58.8%) patients in the vehicle group (6-month masked phase), and 126 (39.0%) patients in the COE 0.1% vehicle extension group during Months 6 to 12 (these were patients in the vehicle group in the masked phase, who switched to COE 0.1% during the extension)- Table 10 below. In the Special senses body system (mostly eye AEs), AEs were reported for 177 (40.6%), 207 (47.4%), 134 (30.3%) and 72 (23.3%) patients in the COE 0.05%, COE 0.1%, vehicle and COE 0.1% vehicle extension groups, respectively. Burning eye was the most common AE, reported for 82 (18.8%), 83 (19.0%), 33 (7.5%) and 26 (8.0%) patients in the COE 0.05%, COE 0.1%, vehicle and COE 0.1% vehicle extension groups, respectively.

Table 10

COSTART Body System Preferred Term	Number (%) of Patients			
	COE 0.05%, 12 months N = 436	COE 0.1%, 12 months N = 437	Vehicle [a] 6 months N = 442	COE 0.1% VE Months 6-12 [b] N = 323
Overall	281 (64.4)	299 (68.4)	260 (58.8)	126 (39.0)
Body as a whole	93 (21.3)	86 (19.7)	97 (21.9)	29 (9.0)
Infection	29 (6.7)	28 (6.4)	37 (8.4)	7 (2.2)
Headache	18 (4.1)	21 (4.8)	15 (3.4)	6 (1.9)
Flu syndrome	16 (3.7)	10 (2.3)	17 (3.8)	3 (0.9)
Cardiovascular	36 (8.3)	39 (8.9)	20 (4.5)	11 (3.4)
Hypertension	16 (3.7)	9 (2.1)	7 (1.6)	1 (0.3)
Special senses	177 (40.6)	207 (47.4)	134 (30.3)	72 (22.3)
Burning eye	82 (18.8)	83 (19.0)	33 (7.5)	26 (8.0)
Irritation eye	18 (4.1)	11 (2.5)	8 (1.8)	5 (1.5)
Hyperemia conjunctival NOS	17 (3.9)	25 (5.7)	10 (2.3)	10 (3.1)
Discharge eye	15 (3.4)	10 (2.3)	8 (1.8)	1 (0.3)
Foreign body sensation	14 (3.2)	13 (3.0)	10 (2.3)	3 (0.9)
Pain eye	13 (3.0)	32 (7.3)	18 (4.1)	6 (1.9)
Visual disturbance	12 (2.8)	20 (4.6)	19 (4.3)	3 (0.9)
Pruritus eye	11 (2.5)	25 (5.7)	11 (2.5)	4 (1.2)
Photophobia	10 (2.3)	10 (2.3)	4 (0.9)	0
Stinging eye	10 (2.3)	22 (5.0)	10 (2.3)	7 (2.2)

COE = ciclosporin ophthalmic emulsion ; COSTART = Allergan modified Coding Symbols for a Thesaurus of Adverse Reaction Terms; ITT = Intent to treat population; VE = vehicle extension

[a] Adverse events from Months 1 to 6 for patients who received vehicle in 1st 6 months of study.

[b] Adverse events from Months 6 to 12 for patients who had received vehicle in during 1st 6 months of study.

During clinical development, some terms were changed in the Allergan modified COSTART dictionary (e.g., "burning sensation in eye" rather than "burning eye"); the preferred term used in the clinical study report is the term used in the summary table.

Source: Module 5.3.5.3, ASA, Table 28.1

Treatment-Related Adverse Events, 192371-002, -003, and -501, 12-Month Pooled Data

In the pooled analysis of safety (Studies 192371-002, -003 and -501), treatment-related AEs were reported for 127 (29.1%), 150 (34.3%), 93 (21.0%) and 44 (13.6%) patients in the COE 0.05% (12-month), COE 0.1% (12-month), vehicle (Months 1 to 6) and COE 0.1% vehicle extension (Months 6 to 12) groups, respectively (Table 10). Special senses (eye) AEs were reported for 118 (27.1%), 145 (33.2%), 85 (19.2%) and 41 (12.7%) in the COE 0.05%, COE 0.1%, vehicle and COE 0.1% vehicle extension groups, respectively; the most frequently reported treatment-related AE was burning eye, which was reported for 74 (17.0%), 74 (16.9%), 29 (6.6%) and 21 (6.5%) patients, respectively. Additional treatment-related special senses (eye) AEs reported for ≥ 3% of patients were irritation eye, hyperaemia conjunctival NOS, pain eye, stinging eye, pruritus eye, and visual disturbance.

Table 11

COSTART Body System Preferred Term	Number (%) of Patients			
	COE 0.05%, 12 months N = 436	COE 0.1%, 12 months N = 437	Vehicle [a] 6 months N = 442	COE 0.1% VE (Months 6-12) [b] N = 323
Overall	127 (29.1)	150 (34.3)	93 (21.0)	44 (13.6)
Special senses	118 (27.1)	145 (33.2)	85 (19.2)	41 (12.7)
Burning eye	74 (17.0)	74 (16.9)	29 (6.6)	21 (6.5)
Irritation eye	13 (3.0)	10 (2.3)	7 (1.6)	5 (1.5)
Hyperemia conjunctival NOS	11 (2.5)	18 (4.1)	9 (2.0)	7 (2.2)
Pain eye	10 (2.3)	22 (5.0)	11 (2.5)	5 (1.5)
Stinging eye	10 (2.3)	19 (4.3)	9 (2.0)	7 (2.2)
Pruritus eye	8 (1.8)	16 (3.7)	7 (1.6)	2 (0.6)
Visual disturbance	8 (1.8)	14 (3.2)	12 (2.7)	1 (0.3)

COE = ciclosporin ophthalmic emulsion; COSTART = Allergan modified Coding Symbols for a Thesaurus of Adverse Reaction Terms; ITT = Intent to treat population; VE = vehicle extension

Treatment-related: Relationship to treatment - possibly, probable, definite

[a] Adverse events from Months 1-6 for patients who received vehicle in 1st 6 months of study.

[b] Adverse events from Months 6-12 for patients who had received vehicle in during 1st 6 months of study.

During clinical development, some terms were changed in the Allergan modified COSTART dictionary (e.g., "burning sensation in eye" rather than "burning eye"); the preferred term used in the clinical study report is the term used in the summary table.

Source: Module 5.3.5.3, ASA, Table 30.1

Ocular burning

The overall incidence of adverse events irrespective of causality was similar for COE and vehicle apart from burning eye which, in the 12 month pooled safety data occurred in 18.8% and 19.0% of patients treated with COE 0.05% and 0.1% respectively, compared with 7.5% of patients in the vehicle group. This was mirrored in treatment-emergent adverse events with an incidence of burning eye of 17% with COE 0.05% and 6.6% with vehicle.

The Applicant's summary of clinical safety presents a breakdown of safety data in the first 6 months compared to the 6-12 month extension phase from studies -002 and -003 and 6 – 24 months extension phase from study -501 (all patients receiving COE in the extension phases). There was a downwards trend in incidence of burning eye in the COE 0.05% treatment arm in the second 6 months in studies -002 and -003 (1 and 3% cf ~17% in the first 6 months).

Discontinuations attributed to ocular burning were less than 5%, likely due to its transience. It has been clarified that the symptom lasts a few minutes after application and tends to diminish over time.

Other symptoms and signs of ocular discomfort:

Other treatment-related ocular AEs with an incidence of 1% to 5% with COE 0.05% or COE 0.1% were irritation eye, foreign body sensation, hyperaemia conjunctival NOS, conjunctivitis NOS, oedema eyelid, epiphora, pain eye, stinging eye, discharge eye, photophobia, pruritus eye, visual disturbance and dry eye. These local irritation symptoms were usually short lasting and occurred at the time COE 0.05% was administered.

Local ocular immunosuppression

Although no signals of local immunosuppression have emerged, such as ocular infection, these potential risks are reflected in the SmPC and the RMP. Section 4.3 includes a contraindication of active peri-ocular as well as ocular infection. Given that patients with DED are susceptible to herpes keratitis due to ocular surface damage**,** Section 4.4 has been amended to include a warning for caution in patients with a history of ocular herpes infection and in patients with active oro-facial herpes. Given that the treatment is intended to be administered long term, the potential risk of long

latency adverse events arising from local ocular immunosuppression has also been reflected in the RMP.

Long term treatment

In the long term extension studies COE 0.05% and COE 0.1% were administered for periods up to 36 months, with the emergence of no additional safety signals.

3.3.8.4. Serious adverse events and deaths

There were a total of 18 deaths (3 who received vehicle and 15 who received COE), none of which were considered to be treatment-related.

It is agreed that the deaths were likely due to co-morbidities which is expected in a population with a mean age of ~60.

Serious adverse events

SAEs in the COE treatment groups were mainly those expected in an older population.

Although there was a low incidence of eye SAEs two patients receiving COE 0.1% developed cataracts in study -501 and one patient receiving COE 0.05% in study 503. Data is provided suggesting the risk of cataract is no higher than background.

3.3.8.5. Laboratory findings

Conjunctival Microbiology in Phase 2 Study

Swabs from the conjunctivas from the lower lids of a subset of patients at selected sites were cultured at baseline (Week 0), end of treatment (Week 12), and 4 weeks post-treatment (Week 16) in Study 192371-001. No significant changes in the microbial ocular flora were observed following treatment with COE.

There were no ocular infections or other clinical signs or symptoms thought to be due to microbial changes in the ocular flora of the COE groups during this study. There was one report of conjunctivitis of unknown aetiology in the vehicle group. There did not appear to be an overgrowth of ocular microorganisms with any of the treatments.

3.3.8.6. Safety in special populations

Table 13

MedDRA Terms	**Age <65** **number (percentage)**	**Age 65-74** **number (percentage)**	**Age 75-84** **number (percentage)**	**Age 85+** **number (percentage)**
Total AEs	161 (55.9)	55 (56.1)	25 (58.1)	3 (42.9)
Serious AEs – Total	15 (5.2)	6 (6.1)	3 (7.0)	1 (14.3)
- Fatal	0	0	1	0
- Hospitalization/prolong existing hospitalization	15 (5.2)	6 (6.1)	1 (2.3)	1 (14.3)
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	N/A	N/A	N/A	N/A
AE leading to drop-out	24 (8.3)	7 (7.1)	6 (14.0)	1 (14.3)
Psychiatric disorders	5 (1.7)	4 (4.1)	0	0
Nervous system disorders	3 (1.0)	4 (4.1)	1 (2.3)	0
Accidents and injuries	8 (2.8)	1 (1.0)	2 (4.7)	1 (14.3)
Cardiac disorders	1 (0.3)	2 (2.0)	0	0
Vascular disorders	6 (2.1)	5 (5.1)	3 (7.0)	0
Cerebrovascular disorders	2 (0.7)	1 (1.0)	1 (2.3)	0
Infections and infestations	48 (16.7)	14 (14.3)	4 (9.3)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	1 (0.3)	0	1 (2.3)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4 (1.4)	3 (3.1)	1 (2.3)	1 (14.3)
<other AE appearing more frequently in older patients>				

3.3.8.7. Discussion on clinical safety

Ciclosporin is a well-known immunosuppressant. Systemic CsA concentrations are largely undetectable following twice daily instillation of COE 0.05% for up to 12 months. Systemic immunosuppression is therefore unlikely.

Whereas systemic immunosuppression is unlikely, the potential for adverse events due to local ocular immunosuppression needs to be fully considered. Local immunosuppression could lead to an increased risk of ocular infection and of long latency events such as corneal and conjunctival neoplasia and peri-ocular malignancy with long term use. Although no signals of local immunosuppression have emerged, such as ocular infection, the potential risks have been reflected in the SmPC and the RMP. Additional important risks in relation to ocular herpes are also included in the RMP. Long latency events including ocular and peri-ocular malignancy are included as risks.

The most common adverse event was “burning eye” which occurred in 17 – 19% of patients treated with COE 0.05% and was rather high also in the vehicle group (~6-8%) . This was transient, occurring immediately after application and diminished with use. Discontinuations attributed to ocular burning were mostly less than 5%.

Concern over the vehicle and castor oil in particular has been allayed.

Data from post-marketing surveillance since COE 0.05% was first launched in 2003 is considered to support that long-term treatment has a favourable safety profile and is well tolerated. There have been no withdrawals of a licence or marketing application based on safety issues.

3.3.8.8. Conclusions on clinical safety

Appropriate risk minimisation in relation to risks of ocular and peri-ocular immunosuppression have been implemented. There are no outstanding safety concerns.

3.4. Risk management plan

The Safety Specification (Part II, SI-SVIII) from RMP version 1.0, dated 31-08-16 was assessed.

The revised safety specification is implemented in RMP version 3.0 dated 04 January 2018.

3.4.1. Safety Specification

The applicant has revised the safety concerns as requested.

Table 16: Summary of the Safety Concerns in RMP version 3.0 dated 04 January 2018

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions to ciclosporin or to any of the excipients
Important potential risks	Ulcerative keratitis Lymphoma and lymphoproliferative disorder Ocular and peri-ocular malignancy Active ocular and peri-ocular infection Ocular herpes reactivation in patients with a history of herpes keratitis

Summary of safety concerns	
	Ocular herpes infection in patients with active oro-facial herpes infection Adverse events in association with off-label paediatric use
Missing information	Use in pregnancy and lactation Use in patients wearing contact lenses

Pharmacovigilance Plan

There are no additional pharmacovigilance (PhV) activities planned or ongoing for Restaysis.

Risk minimisation measures

Only routine risk minimisation measures (RMMs) are planned to minimize the risks of the product in the proposed indication.

Public summary of the RMP

The public summary of the RMP may require revision.

PRAC Outcome

During the plenary meeting held on 29 August – 01 September, the PRAC, having considered the above, agreed by consensus decision that:

- Routine PhV activities are sufficient to identify and characterise the risks of the product in the proposed indication. The PRAC also noted that no additional PhV activities are planned or ongoing;
- The proposed routine RMMs are sufficient to minimize the risks of the product in the proposed indication

3.5. Pharmacovigilance system

The Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC

3.6. New active substance status

N/A

4. Orphan medicinal products

Orphan designation

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

Restaysis is proposed for treatment of moderate dry eye disease in adult patients, including those with Sjögren's disease, which is inadequately controlled despite treatment with tear substitutes or ocular lubricants,

5.1.1. Disease or condition

DED is classed as aqueous tear deficient or evaporative, according to aetiology, although there is overlap in the clinical manifestation and one can lead to the other once the disease is established. Aqueous tear-deficient dry eye (ADDE) results primarily from deficient lacrimal secretion (DEWS, 2007a). Aqueous tear-deficient dry eye includes dry eye from autoimmune Sjögren's syndrome and non-Sjögren's DED. Evaporative DED arises from intrinsic variables such as disorders of lid aperture or low-blink rate, or poor tear quality, leading to a higher rate of evaporation, for example due to Meibomian gland dysfunction.

Regardless of the initiating factors or groups of factors, tear hyperosmolarity is a common final pathway that leads to ocular surface damage and can set in train a cycle of injury-inflammation-injury. Eventually, patients can develop a self-sustaining DED with an unstable and poorly maintained tear film which may develop into more severe forms of DED. Inflammation plays a prominent role in the development and amplification of both the signs and symptoms of the disease.

T cell activation occurs in response to inflammatory cytokine stimulation which in turn sets in train a cycle of immunoinflammation. There is therefore a rationale for ciclosporin, a potent immunosuppressant even where dry eye disease has a primary inflammatory basis. In Sjögren's or other autoimmune disease where immune dysregulation is the primary driver to lacrimal gland dysfunction there may be amplification of the immune-inflammatory loop.

5.1.2. Available therapies and unmet medical need

The treatment of DED aims to achieve improvement in disease signs and symptoms and depends on the severity of the disease. Most patients with mild DED can be treated symptomatically with lubricants/artificial tears for long periods of time. Other therapeutic strategies include ocular inserts, occlusion of the lacrimal puncta, and anti-inflammatory treatment. According to DEWS, patients with moderate to severe DED are recommended to use topical anti-inflammatory drugs such as steroids and ciclosporin, given that many of these patients are inadequately managed by artificial tears and lubricants alone. However, long-term use of corticosteroid eye drops is associated with an increased risk of side effects such as intraocular hypertension, ocular infections and cataract.

Ciclosporin formulations, from 0.05% to 2% ophthalmic emulsions in olive or castor oil, up to four times daily, have been used in EU clinical practice as an off-label alternative to steroids in severe forms of DED for several decades. A 0.1% ophthalmic ciclosporin formulation (Ikervis) was approved for the first time in the EU in January 2015 for treatment of severe keratitis in association with dry eye disease. Ikervis was approved on the basis of evidence of improvement in keratitis without evidence of symptomatic improvement on the grounds that this could help to preserve sight in patients with severe keratitis (EPAR Ikervis EMA/CHMP/473489/2014). Restasis (0.05% ciclosporin) is marketed in 30 countries worldwide In the USA, a 0.05% ciclosporin ophthalmic emulsion (Restasis) is available to increase tear production in patients with ocular inflammation associated with keratoconjunctivitis sicca.

Restasis is available in some EU countries under compassionate use programs. In other countries, pharmacy compounded oily ciclosporin formulations are used.

The therapeutic indication has been revised to be restricted to adult patients with moderate dry eye disease who are not adequately controlled by artificial tears or lubricants.

5.1.3. Main clinical studies

5.2. Favourable effects

The current application is primarily based on a retrospective analysis of a pooled subgroup of patients from three Phase III trials **192731-002, -003 and -501**conducted in the 1990's to investigate COE for the treatment of patients with moderate to severe DED. The original studies were the subject of two previous failed regulatory submissions to Europe. The re-analysis focuses on a subgroup of patients with moderate DED.

Responder analyses:

Total ocular staining responders (co-primary)

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.003) in favour of COE 0.05% versus placebo in the percentage of complete staining responders at 6 months. This was in a minority of the population (12.6%) with 8.9% of patients benefiting over vehicle alone.

Blurred vision responders (co-primary)

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.036) in favour of COE 0.05% versus placebo in the percentage of complete blurred vision responders at 6 months. 49.6% of patients treated with COE 0.05% were complete responders but 37.7% of patients in the vehicle group were complete responders also; therefore an additional ~11.9% of patients only, benefited from the presence of COE. The result was driven primarily by one of the studies (-003) in which 52.9% of patients in the COE 0.05% group versus 27.6% in the vehicle group demonstrated a complete response whereas in study -002 there was a numerical difference in favour of vehicle (40.4% versus 38.5%) indicating heterogeneity of response in this outcome measure between studies.

Schirmer responders (key secondary)

In the pooled subpopulation analysis, in the moderate DED group, there was a statistically significant difference (p = 0.005) in favour of COE 0.05% (17.1%) versus placebo (6.2%) in the percentage of Schirmer responders at 6 months. There was heterogeneity in the proportion of responders across the individual studies, although the same trend for benefit of COE 0.05% over vehicle was present in all (25 % versus 13.7 % in study -002; 17 % versus 1.8% in study -003; and 5.9% versus 2.9% in study -501).

Change from baseline:

Change from baseline data was requested, to inform response in the subgroup populations as a whole.

Moderate DED:

Ocular staining

In the moderate DED subgroup there was a very small treatment difference, in favour of COE 0.05%, in change from baseline total staining score at 6 months (-0.398, 95% CI -0.95, 0.15; p = 0.154). There was a not dissimilar numerical treatment difference for COE 0.05% versus vehicle in the severe DED subgroup (-0.286, 95% CI -0.69, 0.11; p = 0.160). These differences cannot be considered clinically relevant.

For the moderate DED subgroup when ocular staining is evaluated, the low responder rate and small overall change from baseline data indicates heterogeneity within the patient population, with a subset more clearly responsive to 0.05% COE but little evidence of benefit in the remaining patients.

Blurred vision

The moderate DED subgroup data for change from baseline blurred vision also does not support a clinically relevant treatment effect for the subgroup as a whole (treatment difference COE 0.05% versus vehicle, -0.141, 95% CI -0.41, 0.13, p = 0.308), again indicating heterogeneity within the population, with a more responsive subset.

Schirmer score

In the moderate DED subgroup the treatment difference for COE 0.05% is 2.667 mm, 95% CI 1.08, 4.26, p = 0.001, which suggests clinically relevant improvement in tear production in the moderate DED subgroup as a whole. There is a similar benefit with COE 0.1%. Improvement in tear production will be followed by a reduction in tear osmolarity. This supports a trend to a clinically relevant effect in the moderate DED subgroup overall but is not supported by staining or blurred vision outcomes.

Severe DED:

Ocular staining

In severe DED there was consistency between lack of treatment effect for ocular staining in the responder and change from baseline analyses, suggesting a uniformly non-responsive population.

Blurred vision

Unlike the responder analysis, in severe DED there was a nominally significant treatment difference for change from baseline in blurred vision score for COE 0.05% (and with COE 0.1%): for COE 0.05% versus vehicle a treatment difference of -0.246, 95% CI -0.46, -0.03; p = 0.026. This could be explained by a greater sensitivity of the severe DED population to revelation of improvement in blurred vision, given that more patients in the moderate DED subgroup had a blurred vision score of 0 at baseline (were already non-responders) compared with those in the severe DED subgroup. Without accompanying evidence of benefit on ocular staining this cannot be considered sufficient to support benefit of COE 0.05% in the severe DED subgroup.

Schirmer

Patients in the severe DED subgroup fail to demonstrate benefit on tear production with no evidence of a treatment effect for COE 0.05% (or COE 0.1%) on change from baseline tear production by Schirmer score: COE 0.05% vs vehicle, treatment difference 0.712 mm, 95% CI -0.16, 1.58, p = 0.108. This contrasts with the trend to improved tear production in the overall moderate DED patients. The lack of response in severe DED may be understood given a greater likelihood of permanent inflammation-induced fibrotic change in the lacrimal glands in more severe patients which will limit the extent of any improvement in tear production.

Conclusion from comparison of responder and change from baseline data:

In the severe DED subgroup the consistency in lack of treatment effect demonstrated by responder rate and change from baseline analyses, for total staining and Schirmer score, suggests a uniformly non-responsive population. There is heterogeneity of outcome however in the trend to improvement in blurred vision in the overall population. The data as a whole point to Restaysis (COE 0.05% and 0.1%) not being entirely ineffective in severe DED patients but the benefit is insufficient to support an indication in this subgroup.

Whereas, the moderate DED patient population seems to have a more clearly responsive subset, from the responder analyses, and with a trend to clinically relevant improvement in tear production in the overall moderate DED population.

Patients with Sjögrens syndrome

A breakdown of data in Sjögrens and non-Sjögrens patients was requested. In moderate DED, the treatment difference between COE 0.05% and vehicle for complete responder rate in total ocular staining was greater in Sjögren's syndrome patients (17.1%), and reached nominal statistical significance. Whereas in the overall population the responder rate difference was only 8.8%. There was also a 14.9% difference between COE 0.05% and vehicle in blurred vision complete responder rate, compared with a treatment difference of 11.9% in the overall population.

A bigger effect in Sjögrens patients can be understood from a clinical and scientific perspective and supports that ciclosporin is mediating an immunosuppressant action to reduce ocular surface damage. In patients with Sjögrens syndrome the initiating stimulus will be at least in part immune-mediated and is likely to amplify the subsequent cycle of immuno-inflammation.

The treatment difference in the Schirmer's complete responder analysis (normalisation of tear production) was less however in Sjögrens (7.5%) compared with non-Sjögren's patients (10.2%) or the overall population (11.9%). This might be expected given that in patients with Sjögren's syndrome there is more likely to be permanent (inflammation-induced fibrosis and immune-mediated) damage to lacrimal glands. Therefore there is less potential for normalisation of tear production in response to ciclosporin. However, Sjögren's patients will also be susceptible to inflammatory damage to the ocular surface epithelium resulting from inflammatory cytokines released by activated T cells, amenable to ciclosporin-mediated immunosuppressant action and ocular surface repair. Sjögrens patients nonetheless showed a treatment effect of up to 15% when partial Schirmer response was evaluated and is consistent with some improvement in tear production in these patients.

The evidence pointing to a more pronounced efficacy benefit (in both ocular staining and blurred vision) in Sjögren's syndrome patients is accepted and is considered to be in favour of ciclosporin's mechanism of action. The lack of incremental benefit on tear production can be understood and does not undermine the overall efficacy evaluation.

The indication presently specifies patients "including those with Sjögren's disease" which is not in line with CHMP's policy on the wording of the indication. Nonetheless, inclusion of data in Sjögren's patients in section 5.1 is considered informative for the clinician. The phrase "including Sjögrens disease" should be removed from the indication and should be replaced by a cross reference to section 5.1 at the end of the indication statement, in parenthesis "(See section 5.1)

5.3. Uncertainties and limitations about favourable effects

There continues to be substantive concern that the retrospective analysis may have been biased in favour of the study drug.

It is accepted that clinical need was a key motivator of the design of the retrospective analysis. It is hard to exclude however that the design of the retrospective analysis was data-driven in large part. Nonetheless, even if primarily data-driven, this does not immediately invalidate the results obtained from the retrospective analysis but there must be a very strong scientific and clinical rationale to explain the observed inconsistency between endpoints in the original pivotal studies. Endpoints that looked favourable in the original pivotal studies were upgraded for the retrospective analysis whereas others were downgraded. It may be that these choices were data-driven or it may be that knowledge had advanced to support that these were valid choices. How these choices were arrived at originally (whether data-driven or informed by science) is less important than clarifying whether the choices have produced a non-biased outcome or whether they have unduly favoured the drug.

What is important here is not only providing scientific and clinical justification to support the endpoints that were upgraded but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the moderate dry eye patient population. The Applicant has concentrated in the responses thus far, largely on the former. What is needed now is an explicit view to support the clinical and scientific rationale for both upgrading and downgrading of endpoints. In the case of the latter, the downgrading of OSDI, previously assigned as a primary outcome measure, is a focus: why should moderate DED patients not be expected to obtain benefit on this endpoint, when one of the three domains concerns visual function and has 4 questions (reading, driving, computer, TV) when the Applicant asserts that everyday visual functioning is closely related to blurred vision, selected as the sole primary outcome. Also, TBUT and tear osmolarity were downgraded as endpoints. It is not immediately obvious why moderate DED patients would not demonstrate evidence of benefit on these endpoints with ciclosporin.

In the responses to the second list of issues the Applicant provides a reasonably cogent line of reasoning to support the selection of blurred vision as an important outcome measure. This seems to derive in part from expectation of improvement in corneal epithelium which will be important for central vision. The expert statement from Professor Rolando also supports that blurred vision is an important surrogate for tear film quality.

The Applicant is requested to provide a clear and robust justification to support not only why the endpoints that were upgraded would be expected (in the current state of knowledge) to demonstrate efficacy benefit in the proposed target population of moderate dry eye patients; but also why the endpoints that were downgraded would not be expected to produce a result informative of efficacy benefit in the same population.

The following **Major Objection** is raised:

It should be clearly justified that the results across endpoints (favourable and unfavourable), trials, doses, patient populations are consistent with a hypothesis based on sound scientific rationale. There must be sufficient assurance that the design of the retrospective analysis has not biased the outcome in favour of the drug.

5.4. Unfavourable effects

The most common adverse event is ocular burning but this is transient, lasting a few minutes after application, and appears to diminish with continued use and is associated with a low discontinuation rate.

No serious safety signals have emerged and there are no outstanding safety concerns.

Uncertainties and limitations about unfavourable effects

Ciclosporin is a well-known immunosuppressant. Systemic CsA concentrations are largely undetectable following twice daily instillation of COE 0.05% for up to 12 months. Whereas systemic immunosuppression is unlikely, there are potential risks of local ocular and peri-ocular immunosuppression relating to infection and malignancy. These have been addressed with appropriate risk minimisation measures in the SmPC and RMP.

5.5. Effects Table

Table X. Effects Table for Restaysis .

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Total Staining Responders	Co-primary SIGN Stringent threshold	%	12.0%	3.1%	Weak evidence. Questionable clinical relevance. Difference = 8.9% CI 95% 2.9, 14.8 p= 0.003 -small additional percent of responders with COE -difference in mean change from baseline was very small (-0.05 to -0.39 in total staining – scale 0-15) -Ancillary analyses fail to provide reassurance of clinical relevance	Table 2 Section 3.3.6.2.2.
Blurred Vision Responder	Co-primary SYMPTOM Stringent threshold	%	49.6%	37.7%	Weak evidence Questionable clinical relevance Difference = 11.9% CI 95% 0.7, 23.1 p= 0.036 -small additional percent of responders with COE -driven by one study -upgrade to primary endpoint for retrospective analysis in isolation from symptoms of ocular discomfort suggests bias due to prior knowledge	Table 2 Section 3.3.6.2.2

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Schirmer Responders	Secondary Endpoint Normalisation of tear production. Stringent threshold.	%	17.1%	6.2%	Weak evidence Questionable clinical relevance Difference = 10.9% CI 95% 3.3, 18.5 p = 0.005 -small additional percent of responders with COE -heterogeneity across the individual studies -small increase from baseline and SD large	Table 2 Section 3.3.6.2.2
Unfavourable Effects						
Burning eye	TEAE	%	17%	6.6%	Even greater difference in incidence of burning eye compared with REFRESH artificial tears implicates the vehicle at least in part.	
Irritation eye	TEAE	%	3%	1.6%		

5.6. Benefit-risk assessment and discussion

5.6.1. Importance of favourable and unfavourable effects

There is recognised to be an unmet need in patients with moderate dry eye disease who are insufficiently responsive to artificial tears or ocular lubricants. This is a large patient population in the EU.

5.6.2. Balance of benefits and risks

The therapeutic indication is now positioned to be patients with moderate dry eye disease who are inadequately responsive to artificial tears or ocular lubricants.

Patients with moderate DED appear to be heterogenous population, with a relatively small proportion (8.8%) showing clear evidence of benefit for ciclosporin over vehicle in a high stringency outcome: complete resolution of ocular staining, indicating ocular surface repair. A similarly small percentage of patients display improvement in blurred vision, questioned for its validity as a sole symptomatic outcome although acknowledged to be clinically important to visual function. The overall moderate DED population nonetheless displays a trend to clinically relevant improvement in tear production.

Analysis of the severe DED subgroup suggests a uniformly non-responsive population in terms of ocular surface repair and tear production, the latter explicable by a greater likelihood of permanent fibrotic scarring of lacrimal glands in more severe patients. There is heterogeneity of outcome however in the trend to improvement in blurred vision in the overall population.

The data as a whole point to Restaysis (COE 0.05% and 0.1%) not being entirely ineffective in severe DED patients but the benefit is insufficient to support an indication in this subgroup. Whereas, the

moderate DED patient population seems to have a more clearly responsive subset, from the responder analyses, and with a trend to clinically relevant improvement in tear production in the overall moderate DED population.

Although the Sjögrens syndrome subset displays clearer evidence of treatment benefit on ocular staining and blurred vision, it is not considered justified to specify this subset of patients within the indication, on the basis of post-hoc data. Inclusion of Sjögrens data in 5.1 is nonetheless appropriate, to inform the prescriber. The effect in Sjögrens patients is considered to support an immunosuppressant action of the drug.

5.6.3. Additional considerations on the benefit-risk balance

The main outstanding concern is that the retrospective analysis may have been biased in favour of the study drug. Other concerns are considered to have been sufficiently resolved that the benefit-risk could be considered positive if the outstanding major concern in relation to bias can be resolved. This will require the Applicant to put forward a very clear rationale to support the upgrading and downgrading of endpoints for the retrospective analysis and that the heterogeneity between outcomes, trials, patient populations and dose response can also be explained by sound scientific and clinical rationale.
A Major Objection on Clinical grounds is outstanding.

5.7. Conclusions

The overall B/R of Restaysis is negative.