Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Cyclosporin

Proprietary Product Name: Restasis

Sponsor: Allergan Australia Pty Ltd

November 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of Indications, New Dosage Form
Decision:	Withdrawn
Date of Decision:	17 October 2011
Active ingredient(s):	Cyclosporin
Product Name(s):	Restasis
Sponsor's Name and Address:	Allergan Australia Pty Ltd Level 4, 810 Pacific Highway Gordon NSW 2072
Dose form(s):	Eye drops
Strength(s):	200 µg in 0.4 mL (0.5 mg/mL)
Container(s):	0.4 mL plastic ampoule
Pack size(s):	30 ampoules
Route(s) of administration:	Ocular
Dosage:	One drop of Restasis instilled twice a day in each eye approximately 12 hours apart

Product Background

Dry eye disease is one of the most frequently encountered ocular morbidities with available treatments only providing limited temporary symptomatic relief for this disorder. The prevalence of dry eye disease is approximately 1 million Australians ≥ 50 years. In addition, the incidence rate was estimated to be 200,000 new cases of dry eye disease (≥ 50 years) occurring in 2009.

Current treatment options for moderate to moderately severe dry eye disease, such as artificial tears, only alleviate symptoms without addressing the underlying mechanisms of the disease.

Advances in the diagnosis and management of dry eye disease clearly indicate that inflammation of the ocular surface plays a key role in the pathogenesis of dry eye disease. Cyclosporin is a well established immunosuppressive agent. The drug also has antiinflammatory activity. Cyclosporin reduces inflammation by inhibiting T cell activation and down regulating the production of many pro-inflammatory cytokines.

This AusPAR describes a resubmission of an application to extend the indications and register a new dosage form for cyclosporin (Restasis) by Allergan Australia Pty Ltd (the sponsor). The original submission was made in July 2000. The indication proposed in that submission was:

Treatment of keratoconjunctivitis sicca (chronic dry eye disease) to improve tear production and relieve symptoms in patients whose disease is inadequately controlled by tear substitutes.

A full data set was submitted. Following the evaluation of this submission, the sponsor withdrew the application in June 2001. The reason for this was because of "...the deficiencies identified in these reports, in particular the clinical evaluation and comments received from other regulatory authorities." A key problem that was hypothesised at the time was that the vehicle control provided good symptomatic relief.

The clinical data set for the present application essentially consisted of four studies submitted earlier. The main aspect of this submission is a *post hoc* analysis which was conducted on subjects with moderate (Level 2) to moderately severe (Level 3) dry eye disease. This classification of severity is based on the DEWS (dry eye workshop, 2007) classification. This analysis appears to have been undertaken on the advice of the Therapeutic Products Directorate (TPD) Reviewing Division in Canada and an external Reconsideration Panel convened by the TPD. These committees, "concurred that a properly designed and conducted *post hoc* analysis of the clinical trial data in a specific subpopulation could be an acceptable way in which to address the concerns regarding inconsistent efficacy results".

The indication in the current submission is:

Restasis eye drops are indicated for topical anti-inflammatory treatment for dry eye disease which is inadequately controlled with artificial tears.

Regulatory Status

The product received approval in the United States (US) on 23 December 2002 for the indication:

To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

The product received approval in Canada on 19 August 2010 for the indication:

The treatment of moderate to moderately severe (Level 2-3 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. This indication is based on a pooled analysis of a subpopulation of patients from three pivotal studies.

In the European Union (EU) and New Zealand, the registration application was withdrawn prior to approval due to insufficient evidence of efficacy.

II. Quality Findings

Introduction

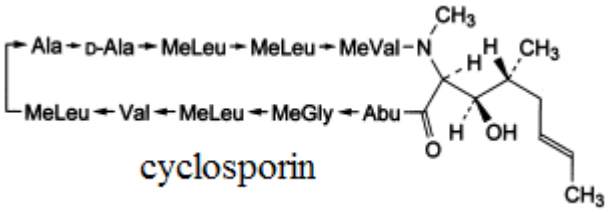
Allergan has reapplied to register Restasis eye drops for use in the treatment of dry eye disease. The recommended dosage is one drop (approximately 27 µL/13.5 µg) of the product instilled twice daily in each eye approximately 12 hours apart.

Cyclosporin oral dosage forms are currently registered by both Sandoz and Novartis as 25, 50 and 100 mg capsules under the tradenames Cicloral (Sandoz), Neoral (Novartis) and Sandimmun (Novartis) for use as an immunosuppressant. Novartis also have registered cyclosporin 50 mg/1 mL and 250 mg/5 mL injection ampoules; a 10 mg cyclosporin capsule and a cyclosporin 100 mg/mL oral solution.

Drug Substance (active ingredient)

The American name is cyclosporine. The international non-proprietary name is ciclosporin. In this AusPAR the product will be referenced as cyclosporin but in future

ciclosporin will be used in Australia. Cyclosporin is a cyclic peptidase of 11 amino acids. It is made by fermentation. It is practically insoluble in water. There are both British Pharmacopoeia (BP) and United States Pharmacopeia monographs for cyclosporin drug substance. Control of the drug substance is considered acceptable.



cyclosporin

Drug Product

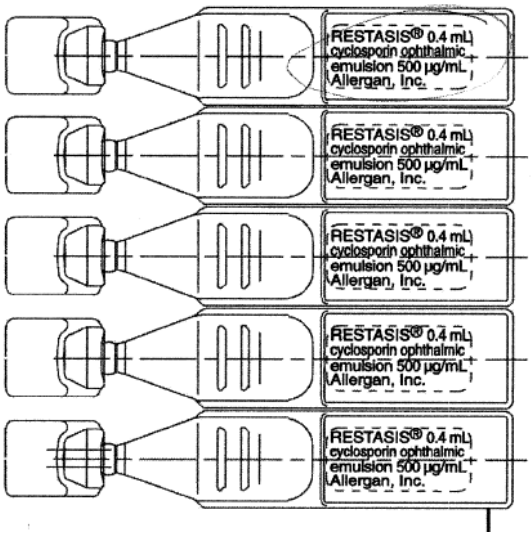
Restasis is a sterile, oil-in-water emulsion of cyclosporin (0.05% w/w). The ampoules contain 200 µg cyclosporin in 0.4 mL; each drop contains about 27 µL or 13.5 µg cyclosporin.

The emulsion is formulated with castor oil, glycerol, polysorbate 80, carbomer copolymer (type A) and water. Sodium hydroxide is used for pH adjustment; the target pH (7.4) is intended to match that of human tears. The formulation is not preserved and each ampoule is intended for single use.

Castor oil itself is not used in other Australian ocular medicines (although the synthetic derivatives hydrogenated-ethoxylated-castor oil and PEG-35 castor oil are used in some.)

There is a BP monograph for Ciclosporin Eye Drops.

The emulsion is packaged (0.4 mL fill) in low density polyethylene (LDPE) unit dose ampoules. The proposed pack size is 30 ampoules presented in a tray with a peelable aluminium foil lid. Ampoules are used after breaking off the cap section (see below).



Biopharmaceutics

Restasis is intended for local action. Systemic blood levels were measured in several trials. For most samples the cyclosporin concentrations were below the limit of quantification (LOQ). The bioanalytical aspects were reviewed in the context of the original application and were considered acceptable.

Advisory Committee Considerations

The original application was considered by the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (which has been succeeded by the Advisory Committee on Prescription Medicines [ACPM]). The reapplication has not been referred to the PSC.

The 78th (2001/3) meeting of the PSC recommended that there should be no objections to approval of the application provided all outstanding issues are addressed to the satisfaction of the TGA.

In addition, the drop size specification for these eye drops should be included in the finished goods specifications or a justification otherwise.

The drop size requirement is not in the BP monograph and is not a regular requirement for eye drops. There is inevitable variation in the delivery of eye drops in use and it is generally accepted that there is a maximum volume which can be usefully be delivered to the eye (about 10-20 μL). The evaluator did not believe that variation in the drop size arising from manufacturing variation of the plastic ampoules will be a significant parameter in variation in ocular exposure. This issue was not pursued.

Quality Summary and Conclusions

Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical Findings

Introduction

This application represents an extension of indication, a new dosage form and a new route of administration for cyclosporin.

Pharmacology

Cyclosporin is a well established immunosuppressant agent, acting to inhibit early events in T-cell activation. The drug also exhibits antiinflammatory activity, mediated by inhibition of the production of pro-inflammatory cytokines or stimulation of the production of antiinflammatory cytokines (Van der Pouw Kraan *et al.*, 1996; Meyer *et al.*, 1997; Pflugfelder, 2004) as well as anti-apoptotic activity, mediated by inhibition of mitochondrial permeability transition pore opening (Zamzami *et al.*, 1996; Friberg *et al.*, 1998).[1,2,3,4,5] The involvement of immune and inflammatory factors in the pathogenesis of dry eye disease provides a rationale for the proposed topical use of cyclosporin. Published studies indicate another potential mechanism for benefit in the condition: the drug increased tear production in dogs and this appears to be a direct lacrimatory effect (rather

[1] Van der Pouw Kraan TC, Boeije LC, Troon JT, Rutschmann SK, Wijdenes J, Aarden LA. Human IL-13 production is negatively influenced by CD3 engagement. Enhancement of IL-13 production by cyclosporin A. J Immunol 1996; 156: 1818–1823.

[2] Meyer S, Kohler NG, Joly A. Cyclosporine A is an uncompetitive inhibitor of proteasome activity and prevents NF-κB activation. FEBS Lett 1997; 413: 354–358.

[3] Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol 2004; 137: 337–342.

[4] Zamzami N, Marchetti P, Castedo M et al. Inhibitors of permeability transition interfere with the disruption of the mitochondrial transmembrane potential during apoptosis. FEBS Lett 1996; 384: 53–57.

[5] Friberg H, Ferrand-Drake M, Bengtsson F, Halestrap AP, Wieloch T. Cyclosporin A, but not FK 506, protects mitochondria and neurons against hypoglycemic damage and implicates the mitochondrial permeability transition in cell death. J Neurosci 1998; 18: 5151–5159.

than being due to immunosuppression), potentially hormonally mediated via prolactin receptors (Kaswan, 1994).[6] Tearing, though, was not a feature of the long term toxicity studies, carried out in rabbits and dogs with the proposed formulation.

One efficacy study was carried out by the sponsor, in which dogs with keratoconjunctivitis sicca (KCS) were treated twice daily (bd) with the proposed cyclosporin emulsion (0.05%) or a higher strength version (0.2%). The animals showed some gross ophthalmic improvement at both dose levels, while reduced accessory lacrimal gland and conjunctival lymphocytic infiltration was evident at the 0.2% strength only. Small increases in tear production (determined using the Schirmer tear test [STT]) were observed (both dose levels) but were not impressive compared with marked enhancements noted in published studies using other formulations. The vehicle itself showed a delayed effect, with little or no difference in STT values between groups of dogs treated with vehicle or 0.05% and 0.2% cyclosporin after 6 weeks. The study also provided evidence for the involvement of lacrimal gland and conjunctival epithelial cell apoptosis in the pathophysiology of canine KCS, with some reversal after 0.2% cyclosporin emulsion treatment (not investigated at 0.05%). Increased tear concentrations of the cytokine transforming growth factor β_1 (TGF-β_1) were evident in dogs with KCS compared with normal animals, with levels reduced in KCS dogs following treatment with 0.2% cyclosporin emulsion.

Overall, topical cyclosporin exhibits beneficial effects in canine KCS, especially as demonstrated in submitted literature publications, one of which used a commercial veterinary preparation (0.2%). Beneficial effects were apparent in the sponsor's study with the proposed formulation in KCS dogs, although histological decreases in lymphocytic infiltration were only apparent with treatment at a higher strength (0.2%) than is proposed for clinical use (0.05%).

Secondary pharmacodynamics and safety pharmacology

No new studies on secondary pharmacodynamics or safety pharmacology were submitted. This was acceptable.

Pharmacokinetics

Ocular tissue distribution studies in rabbits and dogs indicated that topical application of ^{3}H-cyclosporin (in castor oil emulsion) resulted in high concentrations of radioactivity in surface structures (that is, conjunctiva and cornea) but limited ocular penetration, as shown by low aqueous and vitreous humour values. There was no evidence for ocular metabolism of ^{3}H-cyclosporin and the distribution of radioactivity therefore reflected that of the parent drug. Corneal penetration was greater in rabbits compared with dogs and lacrimal gland penetration was higher in dogs. Although the cyclosporin emulsion concentration used in the dog was higher than that proposed for therapeutic use (0.2% compared with 0.05%), multiple dosing achieved a mean lacrimal gland maximum concentration (C_{max}) value that that was more than ten times higher than the median inhibitory concentration (IC_{50}) for cyclosporin's inhibition of mitogen stimulated human lymphocyte proliferation reported in previously evaluated studies (357 ng/g compared with 30 ng/mL). The corresponding peak concentration in the nictitans (accessory lacrimal) gland value was higher (690 ng/g) and would have been high enough to have influenced local lymphocytic function, possibly corresponding to the reduced lymphocytic infiltration seen in the sponsor's efficacy study at this strength (0.2%). Rabbit lacrimal gland C_{max} values after multiple dosing with 0.05% or 0.2% emulsions were relatively low (about 12–15 ng/g); it is not known which of these two species most closely resembles

[6] Kaswan R. Characteristics of a canine model of KCS: effective treatment with topical cyclosporine. In: Lacrimal Gland, Tear Film, and Dry Eye Syndromes. Plenum Press, New York, 1994. (Ed. Sullivan D.A.).

humans for this variable. In terms of corneal concentrations, however, treatment of dogs with another cyclosporin formulation was shown to achieve a similar mean value in dogs and humans but a higher value in rabbits.

Systemic absorption of cyclosporin after ocular application of emulsion concentrations of up to 0.4% bd was very low in humans and only sporadic positive blood values were obtained, using an assay with an LoQ of 0.1 ng/mL. Systemic exposure was also low in rabbits and dogs following topical ocular administration, with peak blood concentrations <1.5 ng/mL in the various pharmacokinetic and toxicity studies. The low blood levels stand in contrast to those obtained in patients treated with oral cyclosporin (for example, blood trough concentrations of ≥75 ng/mL reported with Neoral).

Toxicology

Acute toxicity

The acute toxicity of cyclosporin by the topical ocular route was not investigated. No deaths occurred in rabbits following intravenous (IV) administration of cyclosporin at 14.5 mg/kg, more than 5000 times greater than the maximum recommended daily human dose adjusted for body surface area (assuming 50 kg body weight and bilateral administration in clinical use).[7]

Repeat dose toxicity

Studies of up to 6 months duration were conducted in rabbits and 12 months in dogs using the clinical route. These involved ocular administration of higher strengths and more frequent administration than is proposed clinically (that is, up to six times daily at 0.4% cyclosporin in the pivotal studies). Unilateral administration was used, allowing the untreated eye to serve as a paired control. Rat, dog and monkey studies by the oral route were also submitted; these had been submitted and evaluated in previous applications for oral cyclosporin products. The pivotal studies were Good Laboratory Practice (GLP) compliant. The ophthalmic emulsions used in the studies were formulated as for Restasis apart from the higher strengths of cyclosporin and, to adequately solubilise the drug at 0.2% and 0.4%, higher strengths of castor oil (2 and 4 times greater than for Restasis).

Relative exposure

Exposure ratios obtained in the pivotal toxicity studies have been calculated based on simple comparisons of the daily doses administered to the eye, with high multiples of the maximum clinical dose achieved (see Table 1). Exposure ratios in studies by the oral route have been calculated based on animal:human doses adjusted for body surface area; for humans, bilateral bd use by a 50 kg patient is assumed.

[7] Factors of 3, 6, 15 and 33 have been used to convert mg/kg doses to mg/m^2 ones in mice, rats, rabbits and humans (50 kg), respectively, in this report.

Table 1: Exposure ratios for cyclosporin in toxicology studies

Species	Duration	Drop volume	Treatment (concentration; dosing frequency)		Dose (µg/eye/day)	Exposure ratio
Rabbit (NZW)	6 months	40 µL	0.05%	tds	60	2
			0.2%	tds	240	8
			0.4%	tds	480	17
			0.4%	6×/day	960	34
Dog (Beagle)	12 months	40 µL	0.1%	tds	120	4
			0.2%	tds	240	8
			0.4%	6×/day	960	34
Human; 0.05% bd; 28.5 µL					28.5	–

tds: three times daily

Ocular effects

Treatment with the emulsion was well tolerated, with the only local findings being slight transient hyperaemia and signs of discomfort and conjunctival discharge; detailed histological examinations of ocular tissues did not reveal any effects of the vehicle or cyclosporin.

A concern with long term ocular administration of an immunosuppressant agent such as cyclosporin is the potential for an increase in the incidence or severity of ocular infections. However, such infections were not a feature of the long term toxicity studies; the sponsor's *Clinical Overview* indicates that ocular infections were also absent in patients treated with the cyclosporin emulsion.

Systemic effects

There was no indication of systemic toxicity after ocular treatment, as expected given the limited systemic exposure to cyclosporin following administration by this route. Blood cyclosporin was generally measurable following ocular administration to animals in the toxicity studies; peak blood concentrations at the highest doses used in the pivotal studies were 1.36 ng/mL in the rabbit and 0.675 ng/mL in the dog. In contrast, only sporadic samples gave positive results in the clinical trials and all clinical trial samples with the proposed 0.05% cyclosporin emulsion concentration were negative (<LoQ of 0.1 ng/mL). Thus adequate multiples of the anticipated clinical systemic exposure has been achieved with ocular dosing in the animal studies to identify potential systemic toxicity. Although indices of immunity were not investigated after treatment with the proposed cyclosporin emulsion, the low systemic absorption suggests that this would not be compromised. Supporting this, long term treatment of dogs with a USA registered veterinary cyclosporin ophthalmic ointment (0.2% and 2% bd for 26 weeks) was reported to have no effect on canine distemper and rabies virus antibody responses to vaccination (FDA Approval Summary for Optimmune; NADA 141-052).

The liver, kidney, testes, gingiva and lymphoid tissues were identified as the principal target organs for toxicity by cyclosporin in studies by the oral route. These studies involved doses and systemic exposure levels of cyclosporin far exceeding that relevant to clinical use of Restasis.

Genotoxicity

Cyclosporin was negative in assays for bacterial gene mutation, the mouse micronucleus test, chromosomal aberrations *in vivo* in hamsters and the mouse dominant lethal assay.

Negative results were also returned for cyclosporin in other previously evaluated studies and in experiments reported in the literature (Matter *et al.*, 1982; Ryffel *et al.*, 1983) apart from in an assay for sister chromatid exchange (SCE) induction in human lymphocytes *in vitro*, where a weak positive result was observed at 1 and 5 µg/mL (Yuzawa *et al.*, 1986).[8,9,10] The balance of evidence indicates that cyclosporin does not pose a genotoxic hazard to humans.

Carcinogenicity

Carcinogenicity studies by the oral route were conducted in mice (78 weeks) and rats (95–104 weeks). A trend for increased lymphoma incidence was evident in male and female mice treated at the high dose level (16 mg/kg/day), most likely secondary to immunosuppression. This dose is >1275 times the maximum recommended human dose on a body surface area basis; the highest dose without a tumourigenic effect in mice was 4 mg/kg/day, which is ~320 times the maximum clinical dose adjusted for body surface area. No treatment related increase in tumour incidence was observed in the rat study; the high dose level (8 mg/kg/day) is >1275 times the maximum clinical dose adjusted for body surface area.

Reproductive toxicity

Reproductive and developmental toxicity studies were conducted with cyclosporin using the oral route. The drug (≤15 mg/kg/day) did not affect mating or fertility in male and female rats (~2400 times the maximum recommended human dose adjusted for body surface area). In embryofetal development studies, cyclosporin increased post-implantation loss at maternotoxic doses (at ≥30 mg/kg/day in the rat and ≥100 mg/kg/day in the rabbit) and impaired fetal skeletal development and reduced fetal body weight (at 30 and 100 mg/kg/day in the respective species). No Observable Effect Levels (NOELs) for embryofetal toxicity were 17 mg/kg/day in the rat and 30 mg/kg/day in the rabbit; these doses are approximately 2700 and 12000 times the maximum recommended human dose adjusted for body surface area. The drug did not produce teratogenicity (at ≤30mg/kg/day in the rat and ≤100 mg/kg/day in the rabbit). Adverse effects on renal development have been observed in published studies in rabbits (reported in the Product Information (PI) for other cyclosporin products and in the sponsor's draft PI).

Use in children

Restasis is not proposed for paediatric use and no specific studies in juvenile animals were submitted by the sponsor.

Nonclinical Summary and Conclusions

This application represents an extension of indication, a new dosage form and a new route of administration for cyclosporin. Oral (PO) and IV formulations are currently registered in Australia and provide much higher doses and resultant systemic levels of cyclosporin compared with Restasis.

Cyclosporin is a well established immunosuppressive agent. The drug also has antiinflammatory activity. Efficacy in dry eye disease (keratoconjunctivitis sicca) is suggested by the involvement of immune and inflammatory factors in the pathogenesis of

[8] Matter BE, Donatsch P, Racine RR, Schmid B, Suter W. Genotoxicity evaluation of cyclosporin A, a new immunosuppressive agent. Mutat Res 1982; 105: 257–264.

[9] Ryffel B, Donatsch P, Madörin M etal. Toxicological evaluation of cyclosporin A. Arch Toxicol 1983; 53: 107–141.

[10] Yuzawa K, Kondo I, Fukao K, Iwasaki Y, Hamaguchi H. Mutagenicity of cyclosporine. Induction of sister chromatid exchange in human cells. Transplantation 1986; 42: 61–63.

the condition. Twice daily treatment with the proposed cyclosporin emulsion (0.05%) was shown to produce gross ophthalmic improvement in dogs with keratoconjunctivitis sicca. More impressive efficacy was evident at a higher strength than is proposed for registration (0.2%), including inhibition of lymphocytic infiltration and epithelial cell apoptosis in the lacrimal gland and conjunctiva.

High concentrations of cyclosporin were present in ocular surface structures (conjunctiva, cornea) following topical application of the emulsion to the eyes of rabbits and dogs. Concentrations in the aqueous and vitreous humour were low, indicating limited ocular penetration. The drug was not metabolised in the eye. Systemic absorption after topical ocular administration was very limited in animals and humans.

Repeat dose toxicity studies by the topical ocular route were conducted in rabbits (up to 6 months) and dogs (up to 12 months) and involved higher strengths and more frequent dose administration than is proposed clinically. They revealed the cyclosporin emulsion to be well tolerated in both species, with slight hyperaemia, signs of discomfort and conjunctival discharge the main findings; there were no treatment related ocular histopathological lesions and no evidence of systemic toxicity.

Previously evaluated oral toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies were resubmitted. Effects seen in these studies are expected to be of little relevance to topical ocular use, because of limited systemic absorption.

There were no nonclinical objections to the registration of Restasis for the proposed indication.

IV. Clinical Findings

Introduction

This application included a reanalysis of clinical trial data from studies 002, 003 and 501 previously submitted to the TGA. In addition to the reanalysis, some new trial data have been submitted.

The sponsor indicated that: "The efficacy section of this submission comprises the “intention to treat” (ITT) data from the Phase II dose ranging study (Study 001) conducted in the United States and the three pivotal Phase III efficacy studies conducted in the United States (Study 002 and 003) and in Europe (Study 501).

The Phase II study is included in this submission to provide justification for the dose concentration of cyclosporin (0.05%), for which approval is sought."

Pharmacology

There were no new pharmacokinetic or pharmacodynamic data provided.

Efficacy

Introduction

The reanalysis included in the submission relates to studies 002, 003 and 501, previously submitted to TGA, and described as pivotal studies.

The only new double blind study in the present submission, study 011, was not claimed as pivotal– in fact, it was the subject of very little discussion in the sponsor’s *Clinical Overview* and only an "abbreviated report" was submitted. This may have been because "The entry criteria for Study 011 [were] very different from all other studies; included patients who had more severe disease and worse prognosis compared

with the other studies". However, the entry criteria were not inconsistent with the indications for which registration is now sought.

Dose response studies

Study 001

This study was included in the initial submission so it has been evaluated. It was a Phase II, double blind, parallel group, randomised study performed at 9 centres in the USA. The 0.05% formulation used in it was not that proposed for registration.

Patients were reviewed at 1, 4, 8, 12, 14 and 16 weeks after the start of treatment. Treatment ceased at 12 weeks. Patients were considered evaluable for efficacy if they contributed efficacy data from at least one follow up visit at or after Week 4. Outcome in the ITT population is shown in Table 2.

The planned analysis was the Schirmer tear test, without anaesthesia. Observations relate to the eye with the worse measurement at baseline (Week 0). The among group differences in changes from baseline were not statistically significant (using Kruskal-Wallis test).

Table 2: Schirmer tear test, study 001

		Vehicle	0.05%	0.1%	0.2%	0.4%
Week 0	N	26	27	26	29	27
	Mean (mm)	3.9	3.4	3.8	3.7	3.0
	sd	2.1	2.1	2.1	2.0	2.0
Week 4	N	25	22	23	27	25
	Mean (mm)[1]	5.5	1.6	3.1	2.1	4.0
	sd	8.1	4.9	7.3	7.9	7.3
Week 12	N	25	24	22	26	25
	Mean (mm)[1]	2.6	2.5	3.9	3.0	1.7
	sd	4.9	4.9	7.8	6.4	3.2

[1]Change from baseline

Observations of superficial punctate keratitis (SPK) are shown in Table 3. Observations relate to the average of all areas excluding superior, using the eye with the worse measurement at baseline. The among group differences in categories were not statistically significant (using Kruskal-Wallis test).

Table 3: SPK in study 001

		Vehicle	0.05%	0.1%	0.2%	0.4%
Week 0	N	26	27	26	29	27
	Mean[1]	1.6	1.5	1.7	1.5	1.5
	sd	0.73	0.60	0.74	0.63	0.66
Week 4	N	25	22	23	27	25
	Mean[2]	-0.44	-0.52	-0.79	-0.55	-0.66
	sd	0.67	0.59	0.70	0.49	0.63
Week 12	N	25	24	22	26	25
	Mean[2]	-0.55	-0.65	-0.89	-0.55	-0.82
	sd	0.79	0.76	0.75	0.59	0.80

[1]Scale: 0=None; 1=Mild; 2=Moderate; 3=Severe
[2]Change from baseline. A negative change indicates improvement

Symptoms of dry eye from patient diaries are shown in Table 4. The diary week closest (and prior) to the scheduled visit was used. The scale was: 0=None; 1=Mild; 2=Moderate; 3=Severe; 4=Very severe. The among group differences in changes from baseline were not statistically significant (using Kruskal-Wallis test).

Table 4: Symptoms of dry eye, study 001

		Vehicle	0.05%	0.1%	0.2%	0.4%
Dryness						
Week 0	N	26	27	24	28	27
	Mean[1]	2.4	2.3	2.4	2.5	2.5
	sd	0.99	0.82	0.88	0.79	0.85
Week 12	N	24	23	19	26	24
	Mean[2]	-0.50	-0.56	-0.47	-0.85	-0.79
	sd	0.93	0.84	0.96	1.05	0.98
Sandy or gritty feeling						
Week 0	N	26	27	24	28	26
	Mean[1]	2.0	2.0	2.0	1.7	2.2
	sd	1.09	0.90	1.08	1.21	1.16
Week 12	N	24	23	19	26	23
	Mean[2]					
	sd					
Burning/Stinging						
Week 0	N	26	27	24	28	27
	Mean[1]	1.7	1.7	1.8	1.6	1.6
	sd	1.09	1.27	1.28	0.87	1.05

Week 12	N	24	23	19	26	24
	Mean[2]	-0.33	-0.48	-0.68	0.11	-0.25
	sd	1.27	1.04	1.49	1.03	1.19
Pain						
Week 0	N	26	27	24	28	27
	Mean[1]	1.3	1.0	1.1	1.0	1.0
	sd	1.25	1.14	1.08	1.28	1.14
Week 12	N	24	23	19	26	24
	Mean[2]	-0.21	-0.26	-0.42	-0.11	-0.29
	sd	1.25	0.86	1.07	0.52	1.37
Itching						
Week 0	N	26	27	24	28	27
	Mean[1]	1.5	1.4	1.7	1.9	1.3
	sd	0.99	1.05	1.30	0.80	1.21
Week 12	N	24	23	19	26	24
	Mean[2]	0.0	-0.35	-0.53	-0.61	-0.46
	sd	1.25	1.11	1.07	0.94	0.83
Sensitivity to Light						
Week 0	N	26	27	24	27	27
	Mean[1]	1.6	1.8	2.1	2.2	2.0
	sd	1.39	1.15	0.95	1.27	1.37
Week 12	N	24	23	19	25	24
	Mean[2]	0.04	-0.22	-0.21	-0.24	-0.33
	sd	0.96	0.36	0.50	0.20	0.09

[1]Scale: 0=None; 1=Mild; 2=Moderate; 3=Severe; 4=Very severe.
[2]Change from baseline.

Subgroup analysis

Retrospectively, a number of subgroups were defined and analysed. One of these, designated the "preferred Phase III target population", comprised the 88/162 evaluable patients who had at least 1 eye at baseline with Schirmer ≤ 5 mm and SPK (pupil and nasal average over both eyes) ≥ 1.5. Measurements at Week 12 are shown in Table 5. Results were not statistically significant.

Table 5: Preferred Phase III target population subgroup, study 001

		Vehicle	0.05%	0.1%	0.2%	0.4%
Schirmer	N	14	12	15	15	13
	Mean (mm)[1]	2.0	1.6	2.8	0.5	1.8
	sd	4.5	3.6	5.2	2.4	2.8
SPK	N	14	12	15	15	13
	Mean (mm)[1]	-0.55	-0.42	-1.02	-0.60	-0.92
	sd	0.90	0.82	0.82	0.59	0.72

[1]Change from baseline

Major studies

Study 011

The objective of study 011 was to evaluate the safety and efficacy of cyclosporin (CsA) 0.05% ophthalmic emulsion compared with vehicle for 6 months in patients with moderate to severe KCS. Study participants were patients with moderate to severe KCS. Details are shown in Table 6.

Table 6: Details of study 011

Centres	Design	Objective	Subjects by arm: Treated (Completed *per* protocol)	Gender (Age):	Diagnosis and main inclusion criteria	Primary outcome variables
26 USA; 1 Australia	Phase III, double-blind, parallel group, randomised, vehicle-controlled. 6 months duration	Evaluate the safety and efficacy of Restasis.	Restasis (Res)146 (95); Vehicle (Veh) 144 (95). 1 drop in each eye bd	21M, 269F (mean age 61.6, Standard deviation (sd) 13.5) (in the ITT population)	Patients with moderate to severe KCS. Main inclusion criteria: Sjögren's syndrome or autoimmune connective tissue disease or female ≥ 65; best-corrected ETDRS visual acuity 20/100 or better in each eye; normal lid position and closure.	Temporal interpalpebral conjunctival staining (with Lissamine). Blurred vision.

Methods

The main inclusion criteria were:

- Sjögren's syndrome or autoimmune connective tissue disease or female ≥ 65;
- Schirmer without anaesthesia > 0 and ≤ 7 mm/5 min in one or both eyes (or = 0 and Schirmer with nasal stimulation ≥ 3 mm/5 min);
- sum of corneal and interpalpebral conjunctival staining ≥ 5 (with corneal staining ≥ 2) in same eye as meeting Schirmer criteria;
- best corrected Early Treatment of Diabetic Retinopathy (ETDRS) visual acuity 20/100 or better in each eye;
- normal lid position and closure.

Patients entered a 2 week run-in phase during which time they instilled only *Refresh* artificial tears as needed in each eye. Patients who qualified for the study at Day 0 were then randomised to either cyclosporin 0.05% or vehicle twice daily and continued to use Refresh as needed for 6 months. The randomization was stratified according to Day 0 blurred vision score to ensure approximately equal numbers of patients with similar severity of disease in each treatment group.

Efficacy variables

The stipulated primary efficacy variables were:

- Temporal interpalpebral conjunctival staining (with lissamine) and;
- Blurred vision.

No particular time point was stipulated.

Statistical considerations

Intended enrolment was about 270 patients, in order to obtain ≥ 240 patients with ≥ 1 follow up visit. These numbers were based on results obtained in studies 002 and 003. The protocol stipulated that the trial was to be "double masked" but no further details of blinding were given.

Conjunctival staining

Temporal interpalpebral conjunctival lissamine green staining was to be observed on each eye at screening, Day 0, Months 1, 3, 4.5 and 6 using a 6 point scale of severity (grades 0 to 5). Baseline staining was the value at Day 0 for the worse eye. For each post-baseline visit, a patient was defined as a "success" if the temporal conjunctival staining score for the worse eye is zero. If there were no scheduled or unscheduled visits within the visit window, then the last available observation before the window was carried forward (last observation carried forward [LOCF] method) and used for analysis. Day 0 data (baseline data prior to study medication administration) was not carried forward.

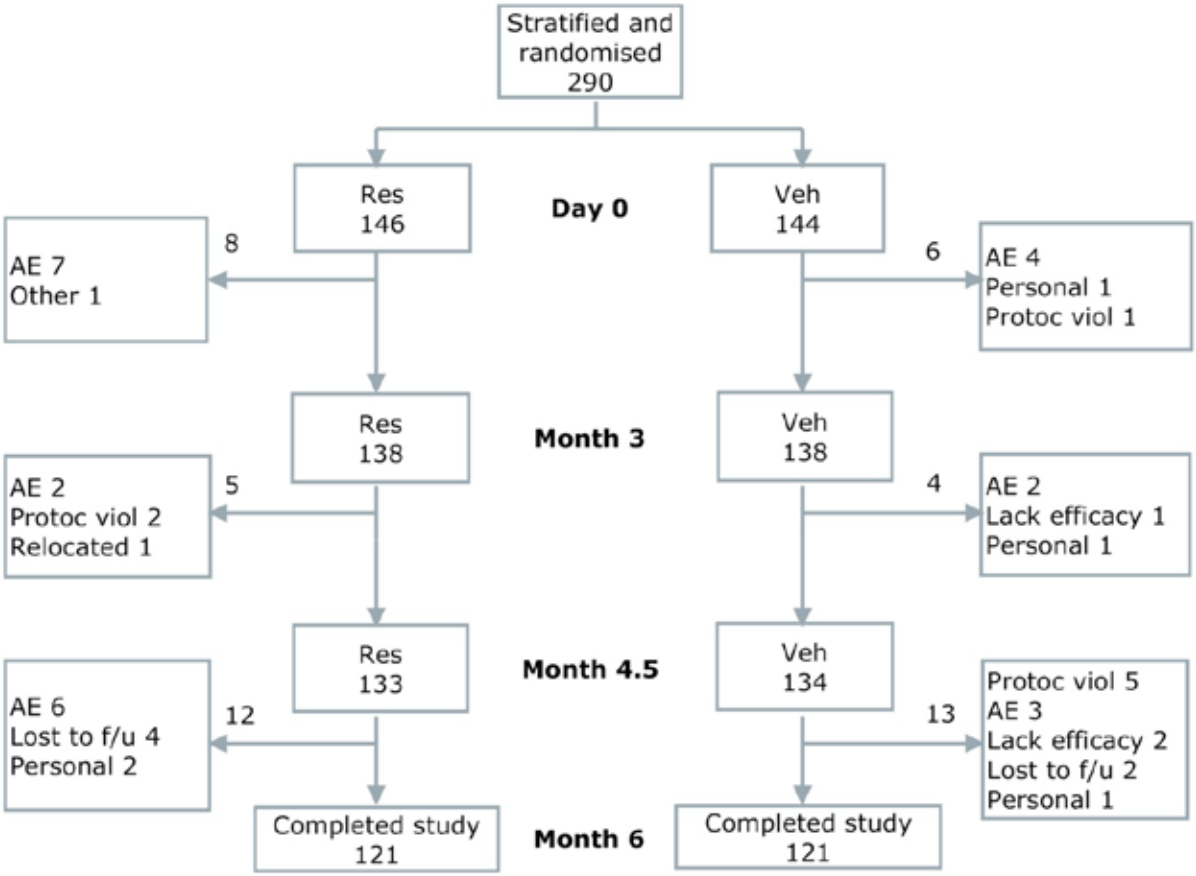
Blurred vision

Symptoms of blurred vision were collected from patients at screening, Day 0, Months 1, 3, 4.5 and 6 using a 5 point scale of severity scale from zero to four. Baseline blurred vision was the value at Day 0. For each post-baseline visit, a patient was defined as a "success" if the blurred vision score is zero. As above, the LOCF methodology was employed except for Day 0 data.

For both measurements, hypothesis of no difference between treatment groups was tested on ITT population using Cochran-Mantel-Haenszel (CMH) test.

The participant flow is shown in Figure 1.

Figure 1: Participant flow, study 011



Outcomes

Conjunctival lissamine green staining

At baseline (Day 0), the mean temporal conjunctival staining was 3.1 in both treatment groups. The change from baseline temporal conjunctival staining at Month 6 was -0.5 in the cyclosporin group and -0.5 in the vehicle group.

Blurred vision

At baseline, the mean blurred vision was 1.9 in the cyclosporin group and 1.7 in the vehicle group. The mean change from baseline at Month 6 was -0.3 in the cyclosporin group and -0.1 in the vehicle group. The percent of patients with a score of 0 at Month 6 was 24.5% (35/143) in the cyclosporin group and 29.3% (41/140) in the vehicle group. These results were not statistically significant.

Double blind extensions of studies submitted previously

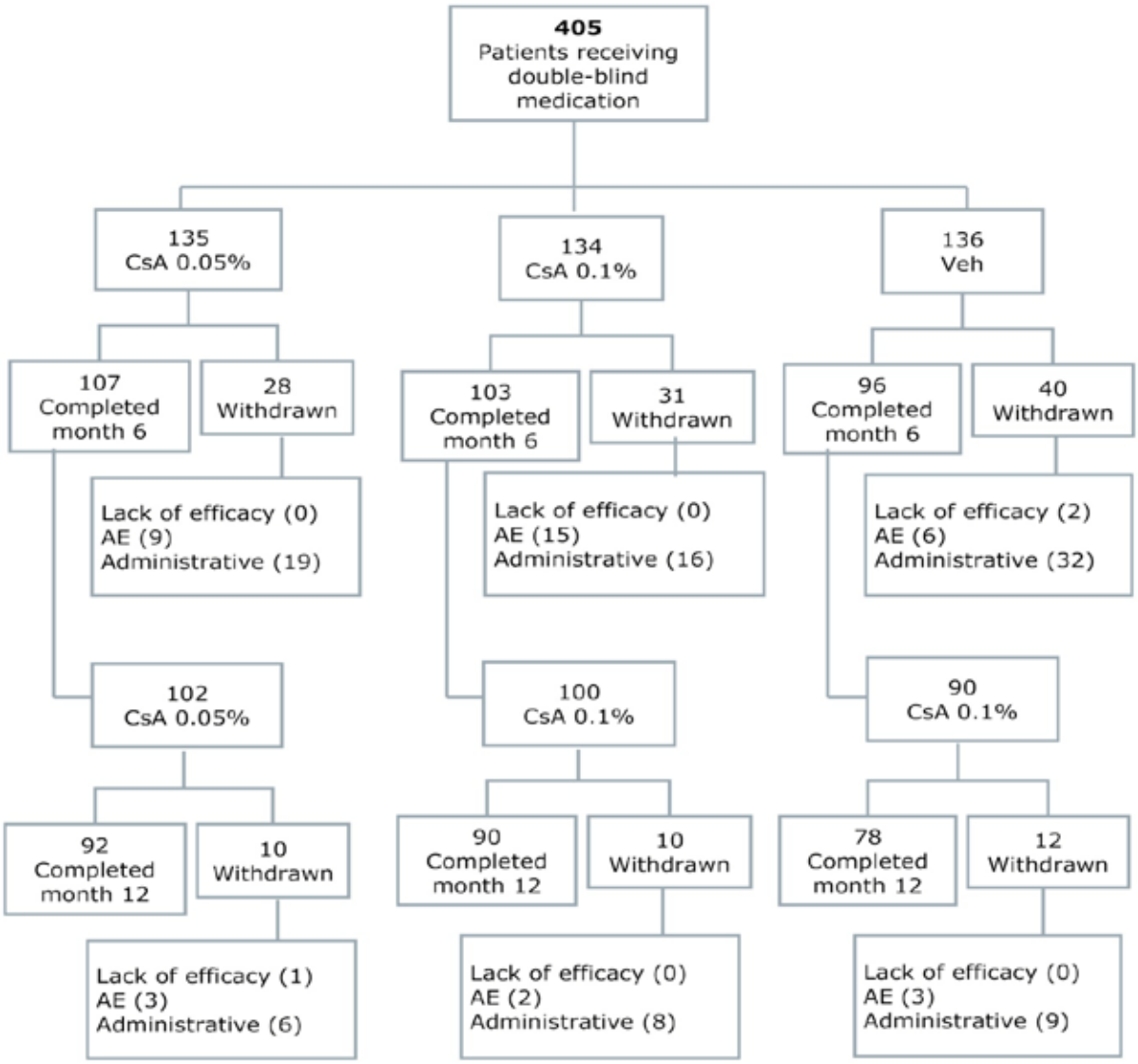
Included in the present submission were reports of the double blind extensions of Phase III studies 002, 003 and 501. Reports on the first 6 months of each of these were evaluated in the initial submission. In these extensions (Months 6-12 for 002 and 003, and Months 6-24 for 501), patients who had been randomised to cyclosporin (CsA) in the double blind, vehicle (Veh) controlled phase continued on the same treatment (either 0.05% or 0.1%), and patients who were randomised to vehicle were changed to cyclosporin 0.1%.

The primary efficacy measures (as stipulated in the protocols) for these studies were: (a) the sum of corneal and interpalpebral conjunctival staining; and (b) Ocular Surface Disease Index (OSDI) score (which ranged from 0=no disability to 1=complete disability).

Study 002

The participant flow is shown in Figure 2.

Figure 2: Participant flow, Study 002



Outcomes

The primary efficacy measures were mean baseline values and mean changes from baseline in the ITT population (Table 7).

Table 7: Changes from baseline in corneal and interpalpebral conjunctival staining and OSDI, study 002

Visit	CsA 0.05%		CsA 0.1%	
	N	Mean (sd)	N	Mean (sd)
Sum of corneal and interpalpebral conjunctival staining				
Baseline (Day 0)	135	7.42 (2.12)	134	7.44 (2.39)
Month 6	129	-2.52 (2.12)	124	-2.13 (2.35)
Month 12	98	-2.66 (2.39)	94	-2.40 (2.31)
OSDI score				
Baseline (Day 0)	135	0.44 (0.21)	134	0.44 (0.21)
Month 6	128	-0.11 (0.20)	124	-0.11 (0.19)
Month 12	97	-0.15 (0.22)	95	-0.16 (0.20)

Study 003

The participant flow is shown in Figure 3.

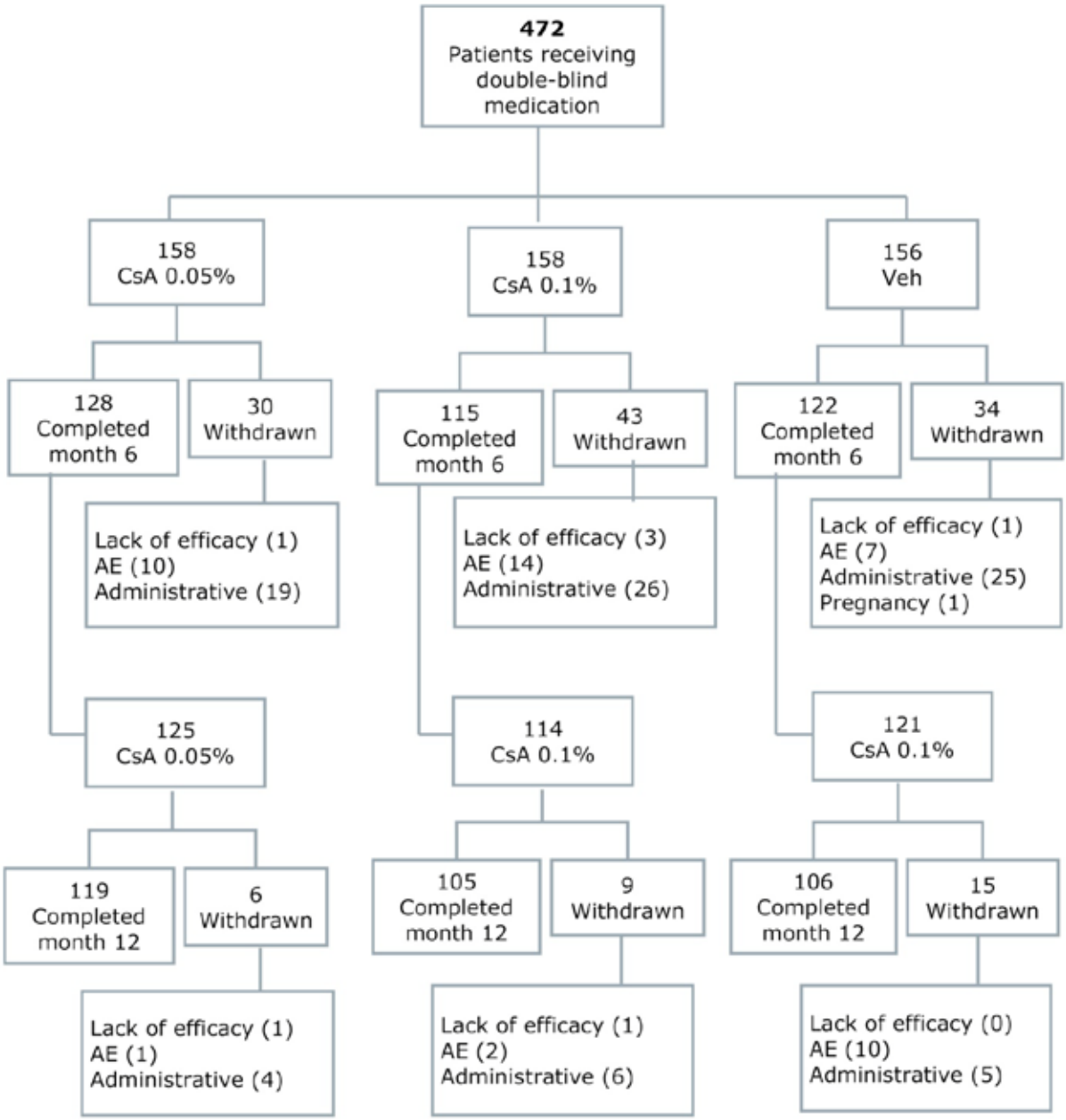
Outcomes

The primary efficacy measures were the mean baseline values and mean changes from baseline in the ITT population (Table 8).

Table 8: Changes from baseline in corneal and interpalpebral conjunctival staining and OSDI, study 003

Visit	CsA 0.05%		CsA 0.1%	
	N	Mean (sd)	N	Mean (sd)
Sum of corneal and interpalpebral conjunctival staining				
Baseline (Day 0)	158	7.46 (2.56)	158	7.40 (2.33)
Month 6	152	-2.22 (2.13)	150	-2.17 (2.47)
Month 12	120	-3.34 (2.40)	111	-3.32 (2.35)
OSDI score				
Baseline (Day 0)	158	0.43 (0.21)	158	0.41 (0.20)
Month 6	152	-0.08 (0.16)	149	-0.09 (0.17)
Month 12	120	-0.10 (0.18)	111	-0.10 (0.17)

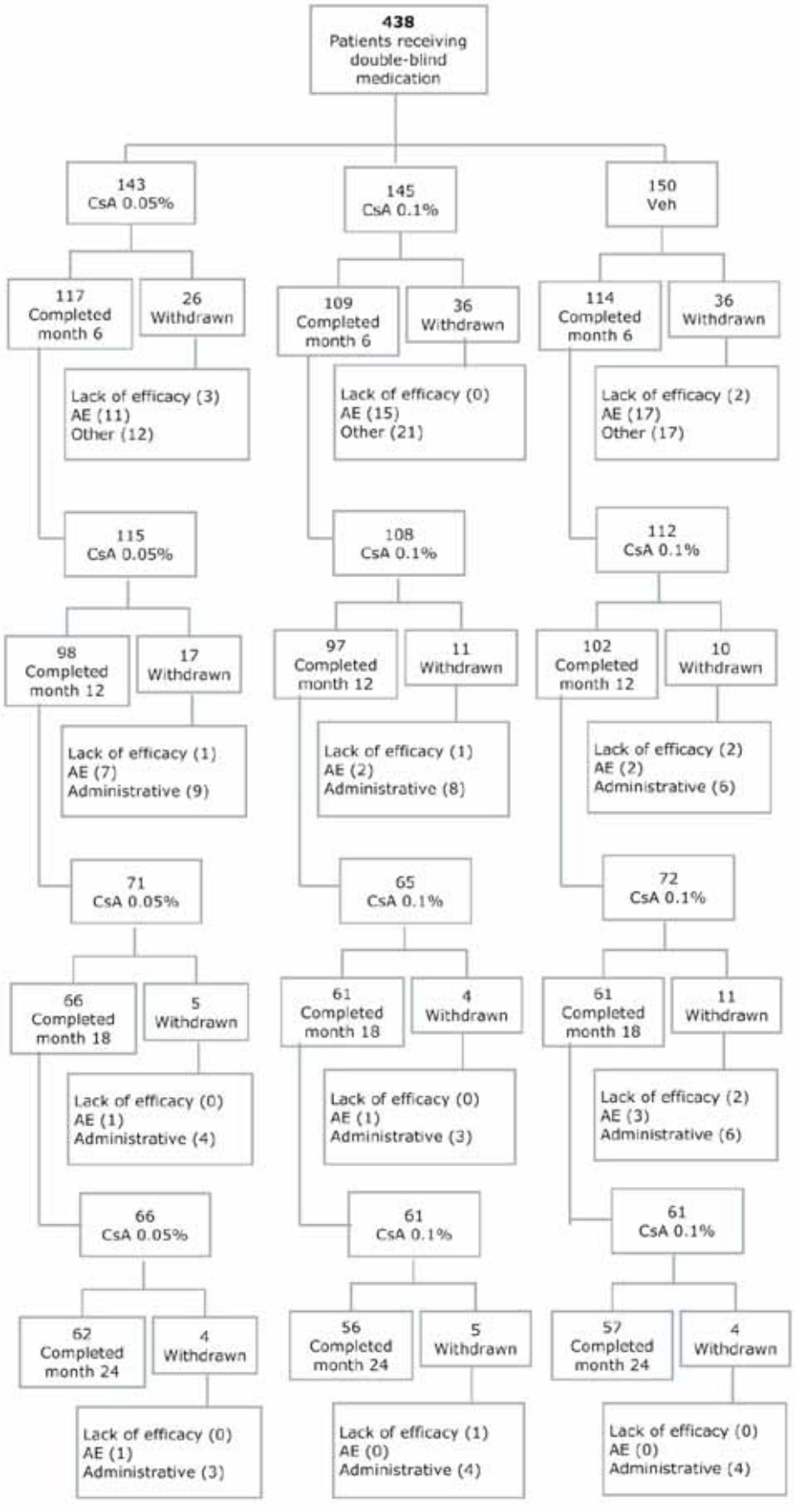
Figure 3: Participant flow, study 003



Study 501

The participant flow is shown in Figure 4.

Figure 4: Participant flow in study



Outcomes

The sponsor's *Clinical Study Report* (CSR) stated that "because the lissamine green staining method was ineffective for determining changes in conjunctival pathology, corneal staining was chosen as the primary variable in the efficacy analysis and not the sum of corneal and interpalpebral conjunctival staining. This was consistent with the FDA submission filed on February 24, 1999." The primary efficacy measures were the mean baseline values and mean changes from baseline in the ITT population (Table 9).

Table 9: Changes from baseline in corneal staining and OSDI, study 501

Visit	CsA 0.05%		CsA 0.1%	
	N	Mean (sd)	N	Mean (sd)
Corneal staining				
Baseline (Day 0)	143	3.01 (0.97)	144	2.97 (0.96)
Month 6	136	-0.73 (1.04)	139	-0.92 (1.01)
Month 12	106	-1.05 (0.96)	101	-1.14 (1.26)
Month 18	106	-1.14 (1.11)	102	-1.25 (1.28)
Month 24	106	-1.30 (1.10)	102	-1.22 (1.30)
OSDI score				
Baseline (Day 0)	143	0.50 (0.21)	144	0.47 (0.20)
Month 6	134	-0.11 (0.20)	136	-0.10 (0.20)
Month 12	101	-0.18 (0.20)	95	-0.15 (0.17)
Month 18	102	-0.17 (0.21)	97	-0.15 (0.18)
Month 24	104	-0.15 (0.21)	98	-0.16 (0.19)

Re-analysis of studies submitted previously

Studies 002, 003 and 501, regarded by the sponsor as pivotal studies and submitted to the TGA in the original application were evaluated in detail at that time. For each of these studies, a subgroup of participants was identified retrospectively (see below) for re-analysis. If any baseline data relevant to the definition of the subgroup were missing, the patient was not included in the subgroup analysis.

The stated rationale for this subgroup analysis was largely as given below.

The subgroup analysis used efficacy variables which differed from the primary efficacy variables stipulated in the protocols. The latter were:

- Sum of corneal and interpalpebral conjunctival staining (corneal evaluation with fluorescein; interpalpebral temporal and nasal conjunctival evaluation with lissamine green).
- The OSDI questionnaire.

The re-analysis, however, focused on the following efficacy variables:

- Total corneal and conjunctival staining (score 0-5 for corneal and 0-10 for conjunctival components). Responders were patients with score 0 at 6 months.

- Schirmer tear test with anaesthesia. Responders defined as those with ≥ 10 mm/5 min at 6 months.
- Blurred vision (score 0 = do not have a symptom to 4 = always notice symptom). Responders were patients with score 0 at 6 months.

The numbers in the groups studied are shown in Table 10.

Table 10: Numbers in the re-analysed subgroups

Study	ITT population		"Level 2-3 subgroup"	
	CsA 0.05%	Veh	CsA 0.05%	Veh
002	135	136	55	61
003	158	156	53	62
501	143	150	40	45
Pooled data	436	442	148	168

Response (in terms of % responders), as measured in the subgroup, compared to response in the full ITT population, is shown in Table 11. All Month 6 data were used even if the visit occurred after the visit window. If no data were available after the baseline visit for a particular variable, then the patient was not included in the analysis for that variable. Whether the other data were analysed on a LOCF basis was not stated.

Table 11: Response in all patients and subgroup patients, studies 002, 003, 501

Efficacy Variable	All patients			Level 2-3 patients		
	CsA 0.05%	Veh	P-value[2]	CsA 0.05%	Veh	P-value[1]
Study 002						
Total corneal and conjunctival staining	3.9	2.4	NS	7.7	1.8	NS
	n = 129	n = 126		n = 52	n = 57	
Schirmer tear test with anaesthesia	17.1	10.1	NS	25.0	13.7	NS
	n = 117	n = 109		n = 48	n = 51	
Blurred vision	25.0	27.6	NS	38.5	40.4	NS
	n = 128	n = 127		n = 52	n = 57	
Study 003						
Total corneal and conjunctival staining	7.9	4.8	NS	19.2	6.9	NS
	n = 152	n = 146		n = 52	n = 58	
Schirmer tear test with anaesthesia	11.7	1.5	<0.001	17	1.8	0.011
	n = 137	n = 134		n = 47	n = 55	
Blurred vision	30.9	25.5	NS	52.9	27.6	0.007
	n = 152	n = 145		n = 51	n = 58	
Study 501						
Total corneal and conjunctival staining	3.7	1.4	NS	7.9	0	NS
	n = 136	n = 144		n = 38	n = 45	
Schirmer tear test with anaesthesia	6.3	4.7	NS	5.9	2.5	NS
	n = 127	n = 129		n = 34	n = 40	
Blurred vision	40.6	42.6	NS	60.5	47.7	NS
	n = 133	n = 141		n = 38	n = 44	
Pooled data						
Total corneal and conjunctival staining	5.3	2.9	NS	12.0	3.1	0.006
	n = 417	n = 416		n = 142	n = 160	
Schirmer tear test with anaesthesia	11.5	5.1	0.002	17.0	6.2	0.007
	n = 381	n = 372		n = 129	n = 146	
Blurred vision	32.2	32.0	NS	40.8	28.4	0.036
	n = 413	n = 413		n = 98	n = 109	

[1] If statistically significant at 0.05.

Supportive studies

Outlines of Studies 505, 005, 502, 006, 007 and 012 are included in this section for convenience, although they relate to safety rather than efficacy.

Study 008

Study 008 was Phase III, investigator blind, parallel group, randomised, vehicle controlled study conducted at 17 centres in the USA and 5 centres in Canada over 3 months. The primary efficacy variable was a ≥ 10% decrease from baseline in sum of corneal and interpalpebral staining. There was also an open label extension over 9 months. Results for the primary variable are shown in Table 12.

Table 12: Efficacy variable, investigator masked period, ITT population, study 008

Efficacy variable	Restasis N=117	Refresh N=118
Combined corneal and conjunctival staining score.[1] Percentage of patients with ≥ 10% decrease from baseline at Month 3.	68.7% (79/115)	64.4% (76/118)

[1] The sum of the corneal and conjunctival scores could range from 0 to 55 (corneal scores from 0 to 25 and conjunctival scores from 0 to 30). Analyses were based on the scores from the worse eye at baseline.

Study 503

Study 503 was a Phase III, investigator blind, parallel group, randomised, vehicle controlled study conducted at centres in Spain (6), Italy (5), Germany (4), UK (4), France (2), Austria, Netherlands, Belgium, Denmark, Finland and Sweden (1 each) over 24 weeks. The primary efficacy variable was a decrease in corneal fluorescein staining of at least one grade at Week 24. There was also an open label extension over 24 weeks. Results for the primary variable are shown in Table 13.

Table 13: Efficacy variable, investigator masked period, ITT population, study 503

Efficacy variable	Restasis N=124	Refresh N=119
Corneal staining score.[2] Percentage of patients with ≥ 1 grade decrease from baseline at week 24.	69.4% (86/124)	68.9% (82/119)

[2] On scale of 0-5.

Other studies

Study 505 was an open label, parallel group, randomised study conducted at 51 centres in France. It was planned as an economic and "humanistic impact" study over 24 weeks.

Study 005 was an open label study over 36 months in centres in France (13), Germany (5), UK (4) and Sweden (1) in patients who had completed either of Studies 002 or 003. The objective was to evaluate safety of CsA ophthalmic emulsion.

Study 502 was an open label study over 24 months in centres in patients who had completed Study 501 within the preceding 90 days with deterioration in visual acuity of ≤ 2 lines since the screening examination of Study 501. The objective was to evaluate the safety of Restasis.

Study 006 was an open label study over 6 months in centres in patients with mild to moderate KCS. The objective was to evaluate safety and efficacy of CsA 0.05%.

Study 007 was an investigator masked, randomized, parallel group study over 6 months in 6 centres in the US and one centre in Australia in patients who experience discomfort while wearing *Hydrogel* contact lenses. The objective was to evaluate safety and efficacy of CsA 0.05%.

Study 012 was planned to be a randomized, double blind, vehicle controlled, parallel-group, 6 week study followed by 52 week open label extension in 4 centres in the US and one centre in Finland in patients with atopic keratoconjunctivitis. The objective was to evaluate safety and efficacy of CsA 0.05% compared to vehicle.

Evaluator's overall conclusions on clinical efficacy

The dose selected

Study 001 is of only preliminary value as a dose ranging study, as the 0.05% formulation used in it is not that proposed for registration. In the opinion of the evaluator therefore, the optimal dosage was not been properly established.

The retrospective subgroup analysis

Central questions for consideration relate to both the internal and external validity of the data and their analysis. Specifically:

(a) The extent to which the sponsor's retrospective analysis of the subgroup data derived from the studies which the sponsor regards as pivotal (that is, 002, 003 and 501) amounts to data dredging.

(b) If the retrospective analysis is regarded as a valid technique in the circumstances, has the sponsor identified a subgroup of patients which is well defined and which in practical therapeutics will enable clinicians to distinguish patients in whom the product may be expected to be beneficial?

Most of the sponsor's *Summary of Clinical Efficacy* relates to the retrospective subgroup analysis. The first part of section focuses on justification of the subgroup analysis. *Inter alia,* this part includes the following text (reference citations omitted):

"The International Task Force (ITF) and Dry Eye Workshop (DEWS) committee evidenced based guidelines for the classification of dry eye disease are based on disease severity and incorporate the symptoms of discomfort and poor vision, as well as clinical signs of the disease. This classification scheme for dry eye disease recommends that topical antiinflammatory medication, such as Restasis, be used for treatment of patients with moderate to moderately severe dry eye disease (Level 2-3) and is not appropriate as a sole therapeutic treatment for patients with severe dry eye disease (Level 4). Given that patients with severe dry eye have end stage, refractory disease, these patients typically require multiple interventions. The DEWS committee further suggest that preliminary experience with Restasis has found that inhibition of the inflammatory factors that adversely impact the ocular surface and tear production early in the course of dry eye disease may prevent the potentially blinding complications associated with dry eye disease.

The original pivotal clinical trials in Allergan's clinical development program were designed to evaluate the use of cyclosporin as monotherapy in a population with fairly severe dry eye disease; a retrospective review of data revealed that more than half of the patients in the clinical development program had severe dry eye disease (Level 4). Not surprisingly, the efficacy results were inconsistent across these original studies, which resulted in the TGA requesting further demonstration of efficacy upon evaluation of Allergan's previous submission in 2000.

This application presents a re-analysis of outcomes from three Phase III, double masked, randomised controlled trials comparing Restasis (0.05% cyclosporin ophthalmic emulsion) with an active vehicle in patients with moderate to severe dry eye disease. These studies were selected on the basis that the study designs and inclusion criteria were sufficiently similar to allow a re-analysis of all patients and two subpopulations (that is, patients with Level 2-3 dry eye disease and patients with Level 4 dry eye disease)."

The grading system used in the text quoted above appears to be that developed by the Management and Therapy Subcommittee of the International Dry Eye Workshop.[11] It is reproduced as Table 14.

Table 14: Dry eye severity grading system

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic occurs under environ stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/ or constant limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

*Must have signs AND symptoms. TBUT: fluorescein tear break-up time. MGD: meibomian gland disease

Reprinted with permission from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. Cornea 2006;25:90-7

In the report of the subcommittee mentioned above, the main evidence cited in relation specifically to the place of cyclosporin in therapy appears to have been derived from some of the very studies Allergan submitted in its original application. Full identifying details are not given, but there is mention of:

- "a Phase II clinical trial, four concentrations of CsA ... 129 patients for 12 weeks was compared to vehicle treatment of 33 patients"; and
- "Two independent Phase III clinical trials ... 877 patients".

The first of these appears to be Study 001 and the other two appear to be Studies 002 and 003. *The sponsor was asked to confirm this.*

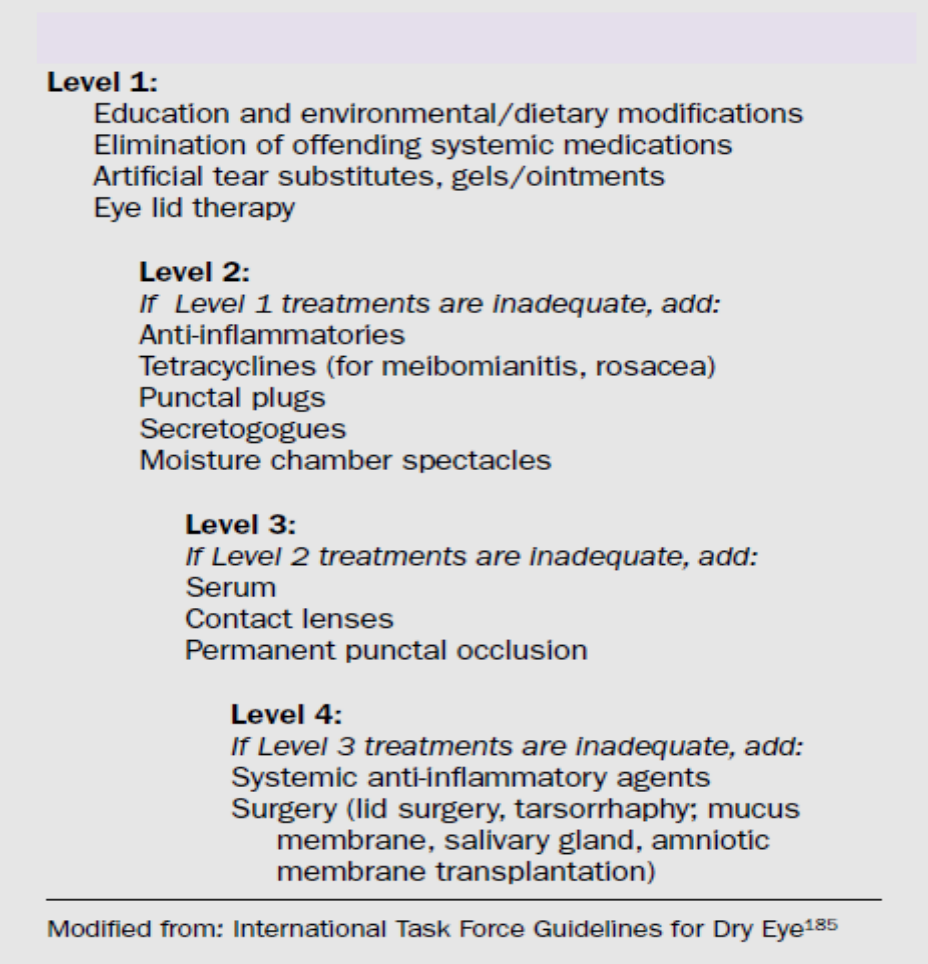
The evaluator did not wish to imply that the sponsor has done anything wrong in putting its data before an expert committee or that the committee lacked expertise. However, the

[11] Management and Therapy Subcommittee. 2007. Management and therapy of dry eye disease: Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop. Ocul Surf 2007; 5: 163-178.

sponsor's argument in justification of the retrospective subgroup analysis of its trial data depends to some extent on the committee's perception of the role of cyclosporin in therapy. To the extent that the committee's opinion was based on the very data which Allergan now seeks to justify re-analysing, the role of the committee must be discounted.

Apart from the specific role of cyclosporin in therapy, the sponsor puts the more general argument (supported by the DEWS) that multiple therapies are required for the worst cases, whereas their main efficacy studies permitted only cyclosporin and lubricant drops. Figure 5 is copied from the above-mentioned subcommittee's report (Management and Therapy Subcommittee 2007). The sponsor calls this in aid of justification of a subgroup analysis which excludes the more severe cases.

Figure 5: Treatment recommendations by severity level



This raises the following questions:

1. Whether it is particularly inappropriate to treat Level 4 patients with only cyclosporin + artificial tears, compared with Levels 2 and 3 patients.
2. The extent to which DEWS Level 4 (the most severe grading defined under the DEWS grading scheme) corresponds to the most severe cases admitted to the studies for which Allergan seeks to justify a subgroup analysis.

3. Whether for the studies in question it is feasible to identify a group of severe cases retrospectively and remove them from the dataset for the purposes of efficacy analysis.

Regarding (1), the evaluator noted that the scheme in Figure 5 is sequential: multiple therapies are envisaged as much for Levels 2 and 3 as for Level 4, in the event of inadequate response.

Regarding (2), the evaluator pointed out that the most severe cases were already excluded from studies 002, 003 and 501 ("Schirmer ... if 0 mm/5 min the Schirmer with nasal stimulation ≥ 3 mm/5 min").

Regarding (3), the opinion of the evaluator was that even prospectively, use of Levels 2-3 in the DEWS grading scheme would be difficult to implement as eligibility criteria for a clinical trial, because of the overlapping nature of some of the criteria and the lack of a specified hierarchy of criteria. Besides, there is a difference between

a) defining inclusion and exclusion criteria, and recruiting patients accordingly; and

b) retrospectively defining a subset of studied patients to be analysed as a subgroup.

Identification of the subgroup for re-analysis

In the sponsor's *Summary of Clinical Efficacy*, the following text appears:

"Three populations were included in the analyses:

1. The ITT population, which comprised all patients who were randomised and received at least one administration of study medication.
2. The DEWS Level 2-3 subpopulation comprised patients who had moderate to moderately severe dry eye disease as defined by the DEWS committee four point severity grading scheme. Patients were included in this group if they had a corneal staining score of 2 to 4, a total staining score of 5 to 9, a Schirmer tear test with anaesthesia score of > 2 mm/5 min, and a blurred vision score < 3.
3. The DEWS Level 4 subpopulation comprised patients who had severe dry eye disease as defined by the DEWS committee four-point severity grading scheme. Patients were included in this group if they had a corneal staining score of 5 to 6, a total staining score of 10 to 15, a Schirmer tear test with anaesthesia score ≤ 2 mm/5 min, and a blurred vision score of 3 to 4."

The sponsor asserted that of the subjects in studies 002, 003 and 501, 284/436 (65.1%) of those treated with cyclosporin 0.05% and 271/442 (61.3%) of those treated with vehicle were DEWS Level 4. This appears to be based on the loose interpretation of the DEWS grading scheme copied immediately above and in the view of the evaluator, the claim that the subgroup analysis was conducted on a group defined in accordance with the DEWS grading scheme is not justified. Rather, it appears that the sponsor has used its own criteria to distinguish retrospectively the subgroup "severe" among patients who had participated in the studies and so exclude from the efficacy analysis nearly two thirds of participants. It was also noted that the "corneal staining score of 5 to 6" above appears to be an error, as the maximum score in the studies was 5.

Summary

The argument that the subgroup selection was justified by advancing science or by other factors extrinsic to the data produced by the studies is weak. Use of different efficacy variables further diminishes the value of the re-analysis.

The opinions of the evaluator in relation to the two central questions posed at the beginning of this section are:

(a) The evaluator did not believe an adequate justification has been given for the retrospective subgroup analysis.

(b) Even if the subgroup analysis had been technically valid, the evaluator did not believe the sponsor has identified a subgroup of patients which is well defined and which in practical therapeutics would have enabled clinicians to distinguish patients in whom the product may be expected to be beneficial.

New data

The outcome of Study 011 does not provide any substantial evidence of efficacy. The additional double blind data from Studies 002, 003 and 501 are not suggestive of a difference in response between 0.05% and 0.1% CsA.

The outcomes of Studies 008 and 503 contribute no substantial evidence of efficacy.

Safety

Introduction

The safety evidence presented (in addition to that included in the original application) comprises:

- data from the new studies
- data from the Periodic Safety Update Reports (PSURs).

Patient exposure

The Phase II and III studies in moderate to severe dry eye disease (including those submitted in the original application) provided a safety database of 2310 patients, of whom 1757 had been exposed at least once to any concentration of CsA ophthalmic emulsion.

Treatment exposure for patients receiving 0.05% CsA in studies 001, 002, 003, 008, 011, 501, 502, 503 and 505 is shown in Table 15.

Table 15: Exposure in studies 001, 002, 003, 008, 011, 501, 502, 503 and 505

Exposure	CsA 0.05% (N=1174) n (%)
At least 1 day	1149 (97.9)
At least 28 days	1102 (93.9)
At least 84 days	1000 (85.2)
At least 168 days	858 (73.1)
At least 252 days	579 (49.3)
At least 336 days	480 (40.9)
At least 504 days	132 (11.1)
At least 840 days	88 (7.5)
At least 1008 days	52 (4.4)

Adverse events

Major efficacy studies and major safety studies

Adverse events (AEs) relating to these studies are displayed separately, as follows:

Study 011: AEs are shown in Table 16, classified by Body System.

Table 16: AEs by Body System, study 011

Body System[1]	Res (n=146)		Veh (n=144)	
Preferred Term	**n**	**%**	**n**	**%**
Patients with one or more AEs	101	69.2	85	59.0
Body as a Whole	35	24.0	29	20.1
Infection	11	7.5	7	4.9
Accidental injury	6	4.1	5	3.5
Back pain	6	4.1	4	2.8
Allergic reaction	4	2.7	3	2.1
Headache	1	0.7	3	2.1
Leg pain	0	0.0	3	2.1
Cardiovascular System	15	10.3	5	3.5
Hypertension	9	6.2	3	2.1
Digestive System	6	11.0	10	6.9
Periodontal abscess	3	2.1	1	0.7
Dyspepsia	2	1.4	4	2.8
Endocrine System	2	1.4	2	1.4
Haemic and Lymphatic System	2	1.4	2	1.4
Metabolic and Nutritional Disorders	4	2.7	2	1.4
Musculoskeletal System	10	6.8	8	5.6
Arthritis	4	2.7	2	1.4
Bone fracture - cause unknown	3	2.1	3	2.1
Nervous System	3	2.1	7	4.9
Respiratory System	17	11.6	23	16.0
Bronchitis	8	5.5	1	0.7
Rhinitis	3	2.1	2	1.4
Cough increased	3	2.1	0	0.0
Pneumonia	3	2.1	0	0.0
Infection sinus	1	0.7	8	5.6
Pharyngitis	0	0.0	6	4.2
Skin and Appendages	5	3.4	5	3.5
Special Senses	49	33.6	39	27.1
Burning sensation in eye	15	10.3	5	3.5
Irritation eye	5	3.4	4	2.8
Visual disturbance	4	2.7	5	3.5
Photophobia	4	2.7	4	2.8
Urogenital System	9	6.2	12	8.3

[1]Each AE is included in a Body System count. Only selected Preferred Terms are shown, but all those reported by > 2% patients in either group are included. Within a Preferred Term, a patient is counted at most once.

Study 002, 6 month double blind extension: AEs starting during this period and considered treatment related: overall and reported (Preferred Term [PT]) by ≥3% of patients in any of the three treatment groups, are shown in Table 17, classified by Body System.

Table 17: Treatment related AEs by Body System, study 002, double blind extension

Body System	CsA 0.05% (n=102)		CsA 0.1% (n=100)		Veh/CsA 0.1% (n=90)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Patients with one or more AEs	4	3.9	11	11.0	11	12.2
Special Senses	3	2.9	10	10.0	10	11.1
Burning eye	0	0.0	4	4.0	6	6.7

Study 003, 6 month double blind extension: AEs starting during this period and considered treatment related: overall and reported (PT) by ≥3% of patients in any of the three treatment groups, are shown in Table 18, classified by Body System.

Table 18: Treatment related AEs by Body System, study 003, double blind extension

Body System	CsA 0.05% (n=125)		CsA 0.1% (n=114)		Veh/CsA 0.1% (n=121)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Patients with one or more AEs	12	9.6	6	5.3	21	17.4
Body as a Whole	0	0.0	0	0.0	1	0.8
Skin	2	1.6	0	0.0	0	0.0
Special Senses (ocular)	11	8.8	6	5.3	20	16.5
Conjunctival hyperaemia	0	0.0	1	0.9	4	3.3
Stinging eye	0	0.0	1	0.9	5	4.1
Burning eye	4	3.2	3	2.6	12	9.9

Study 501, 18 month double-blind extension: Numbers of patients with AEs during the whole 2 year study are consolidated in Table 19.

Table 19: AEs by Body System, study 501, first 6 months, plus 18 month double blind extension

	CsA 0.05%		CsA 0.1%		Veh/ CsA 0.1%			
	(months 0-24)		(months 0-24)		CsA 0.1% (months 6-24)		Veh (months 0-6)	
Body System[1]	n=143		n=145		n=112		n=150	
Preferred Term	n	%	n	%	n	%	n	%
Patients with one or more AEs	110	76.9%	106	73.1	65	58.0	93	62.0
Special Senses	**68**	**47.6%**	**74**	**51.0%**	**37**	**33.0%**	**48**	**32.0%**
Burning eye	36	25.2%	25	17.2%	11	9.8%	12	8.0%
Conjunctivitis	8	5.6%	7	4.8%	2	1.8%	3	2.0%
Hyperaemia conjunctival	7	4.9%	10	6.9%	2	1.8%	7	4.7%
Irritation eye	6	4.2%	6	4.1%	2	1.8%	2	1.3%
Pain eye	6	4.2%	14	9.7%	4	3.6%	10	6.7%
Pruritus eye	3	2.1%	12	8.3%	4	3.6%	1	0.7%
Blepharitis	1	0.7%	5	3.4%	1	0.9%	1	0.7%
Stinging eye	0	0.0%	6	4.1%	0	0.0%	5	3.3%
Body as a Whole	**33**	**23.1%**	**28**	**19.3%**	**25**	**22.3%**	**34**	**22.7%**
Infection	7	4.9%	4	2.8%	2	1.8%	7	4.7%
Headache	5	3.5%	7	4.8%	1	0.9%	8	5.3%
Asthenia	3	2.1%	2	1.4%	2	1.8%	8	5.3%
Flu syndrome	3	2.1%	6	4.1%	4	3.6%	4	2.7%
Respiratory System	**25**	**17.5%**	**23**	**15.9%**	**15**	**13.4%**	**13**	**8.7%**
Pharyngitis	9	6.3%	6	4.1%	3	2.7%	3	2.0%
Rhinitis	6	4.2%	3	2.1%	2	1.8%	1	0.7%
Bronchitis	5	3.5%	6	4.1%	1	0.9%	3	2.0%
Cough increased	2	1.4%	2	1.4%	5	4.5%	1	0.7%
Digestive System	**17**	**11.9%**	**20**	**13.8%**	**10**	**8.9%**	**17**	**11.3%**
Musculoskeletal System	**19**	**13.3%**	**18**	**12.4%**	**4**	**3.6%**	**7**	**4.7%**
Arthralgia	5	3.5%	8	5.5%	0	0.0%	2	1.3%
Arthritis	3	2.1%	8	5.5%	0	0.0%	3	2.0%
Urogenital System	**14**	**9.8%**	**10**	**6.9%**	**9**	**8.0%**	**8**	**5.3%**
UTI	8	5.6%	5	3.4%	1	0.9%	3	2.0%
Cardiovascular System	**10**	**7.0%**	**18**	**12.4%**	**8**	**7.1%**	**5**	**3.3%**
Hypertension	4	2.8%	6	4.1%	3	2.7%	0	0.0%
Nervous System	**11**	**7.7%**	**10**	**6.9%**	**3**	**2.7%**	**14**	**9.3%**
Dizziness	5	3.5%	0	0.0%	1	0.9%	1	0.7%
Skin	**11**	**7.7%**	**7**	**4.8%**	**5**	**4.5%**	**9**	**6.0%**
Metabolic and Nutritional	**4**	**2.8%**	**8**	**5.5%**	**5**	**4.5%**	**2**	**1.3%**
Haemic and Lymphatic	**3**	**2.1%**	**2**	**1.4%**	**1**	**0.9%**	**1**	**0.7%**
Endocrine	**1**	**0.7%**	**1**	**0.7%**	**0**	**0.0%**	**1**	**0.7%**

[1]Each AE is included in a Body System count. Only selected Preferred Terms are shown, but all those reported by ≥ 3% patients in any treatment group are included.

Within a Preferred Term, a patient is counted at most once.

Other studies

Study 008

AEs are shown in Table 20.

Table 20: Number (%) of patients with AEs classified as treatment related, reported by ≥ 1% of patients in either group

	3-month controlled period		9-month extension period	
Body System **Preferred Term**	**CsA 0.05%** **N = 122**	**Refresh** **N = 118**	**CsA 0.05%** **N = 90**	**Refresh/ CsA 0.05%** **N = 97**
Overall	25 (20.5)	6 (5.1)	10 (11.1)	23 (23.7)
Digestive system				
Diarrhoea				1 (1.0)
Special senses				
Burning sensation in eye	15 (12.3)		4 (4.4)	12 (12.4)
Stinging sensation eyes	6 (4.9)	1 (0.8)	3 (3.3)	4 (4.1)
Conjunctival hyperaemia	3 (2.5)			4 (4.1)
Irritation eye	3 (2.5)			2 (2.1)
Eye pruritus	2 (1.6)	1 (0.8)		3 (3.1)
Eye pain	1 (0.8)	1 (0.8)		5 (5.2)
Visual disturbance	1 (0.8)	1 (0.8)	2 (2.2)	2 (2.1)
Blepharoptosis			1 (1.1)	1 (1.0)
Infective conjunctivitis	1 (0.8)		1 (1.1)	
Glaucoma			1 (1.1)	
Keratitis			1 (1.1)	
Photophobia	1 (0.8)	1 (0.8)	1 (1.1)	1 (1.0)
Blepharitis				1 (1.0)
Conjunctivitis				1 (1.0)
Eye discharge	1 (0.8)	1 (0.8)		2 (2.1)
Foreign body sensation				1 (1.0)
Visual acuity worsened				1 (1.0)

Study 503

AEs are shown in Table 21.

Table 21: Number (%) of patients with AEs classified as treatment related, reported by ≥ 1% of patients in either group

	6-month controlled period		6-month extension period	
Body System **Preferred Term**	**CsA 0.05%** **N = 121**	**Refresh** **N = 117**	**CsA 0.05%** **N = 30**	**Refresh/ CsA 0.05%** **N = 33**
Overall	35 (28.9)	18 (15.4)	2 (6.7)	4 (12.1)
Body as a whole				
Headache	2 (1.7)	2 (1.7)		
Special senses				
Burning sensation in eye	20 (16.5)	5 (4.3)	1 (3.3)	
Conjunctival hyperaemia	4 (3.3)	1 (0.9)		3 (9.1)
Erythema eyelid	3 (2.5)	2 (1.7)		
Visual acuity worsened	3 (2.5)	2 (1.7)		
Eye pain	3 (2.5)	1 (0.9)		
Conjunctivitis	2 (1.7)	2 (1.7)		
Eyelid oedema	2 (1.7)	2 (1.7)		
Eye pruritus	2 (1.7)			
Stinging sensation eyes	2 (1.7)			2 (6.1)
Eye discharge		1 (0.9)	1 (3.3)	
Blepharitis				1 (3.0)

Study 505

AEs are shown in Table 22.

Table 22: Number (%) of patients with AEs classified as treatment related, reported by ≥ 1% of patients in either group

Body System **Preferred Term**	**CsA 0.05% + Usual** **N = 32**	**Usual** **N = 28**
Overall	3 (9.4)	0
Special senses		
Burning sensation in eye	3 (9.4)	
Stinging sensation eyes	1 (3.1)	

Study 005

AEs are shown in Table 23.

Table 23: Number (%) of patients with AEs that occurred in ≥ 3% of patients for any body system or for any AE within a body system

Body System AE	CsA 0.1% N = 412
All	269 (65.3)
Special Senses	181 (43.9)
Burning eye	50 (12.1)
Conjunctival hyperaemia	24 (5.8)
Blepharitis	21 (5.1)
Stinging eye	17 (4.1)
Foreign body sensation	14 (3.4)
Eye pruritus	14 (3.4)
Visual disturbance	14 (3.4)
Cataract	13 (3.2)
Visual acuity worsened	13 (3.2)
Body as a Whole	98 (23.8)
Infection	33 (8.0)
Allergic reaction	15 (3.6)
Back pain	13 (3.2)
Digestive	50 (12.1)
Dyspepsia	15 (3.6)
Respiratory	48 (11.7)
Musculoskeletal	42 (10.2)
Arthritis	14 (3.4)
Cardiovascular	40 (9.7)
Hypertension	17 (4.1)
Urogenital	31 (7.5)
Skin and Appendages	30 (7.3)
Nervous	24 (5.8)
Metabolic and Nutritional	21 (5.1)

Study 502

AEs are shown in Table 24. Only PTs occurring in > 2 patients are listed.

Table 24: Number (%) of patients with AEs

Body System Preferred term	Number with AE (%) N=138
Overall	100 (72.5%)
Body as a Whole	
Asthenia	4 (2.9%)
Cardiovascular	
Hypertension	8 (5.8%)
Arrhythmia	3 (2.2%)
Digestive System	
LFTs abnormal	4 (2.9%)
Oral dryness	3 (2.2%)
Metabolic	
Hypercholesterolaemia	4 (2.9%)
Musculoskeletal	
Arthritis	10 (7.2%)
Arthralgia	4 (2.9%)
Bone fracture	3 (2.2%)
Nervous System	
Anxiety	6 (4.3%)
Depression	5 (3.6%)
Respiratory	
Bronchitis	4 (2.9%)
Rhinitis	3 (2.2%)
Skin and Appendages	
Eczema	3 (2.2%)
Special Senses	
Burning sensation eye	18 (13.0%)
Cataract	9 (6.5%)
Eye pain	7 (5.1%)
Conjunctivitis	4 (2.9%)
Eye pruritus	3 (2.2%)
Inflammation eye	3 (2.2%)
Macular degeneration	3 (2.2%)
Tear film abnormality	3 (2.2%)
Urogenital	
Urinary incontinence	3 (2.2%)
UTI	3 (2.2%)

Studies for other indications

Study 006

Most of the report was missing from the submission and the evaluation was done on the available submitted data. In the open phase, AEs occurred in 37/127 patients (5 burning sensation eye, 5 eye pain, 5 foreign body sensation eye, others). In the controlled phase, AEs occurred in 12/56 patients on CsA (3 colds, 2 foreign body sensation eye, others) and 5/57 on Refresh.

Study 007

AEs are shown in Table 25. Only AEs that occurred for ≥ 5% of patients in either treatment group for any Body System or for any AE within a Body System are listed.

Table 25: Number (%) of patients with AEs

Body System **AE**	**CsA 0.05%** **N = 41**	**Lubricant** **N = 39**
Overall	28 (68.3%)	21 (53.8%)
Special senses	17 (41.5%)	14 (35.9%)
Burning eye	7 (17.1%)	1 (2.6%)
Conjunctival hyperaemia	5 (12.2%)	6 (15.4%)
Eye pain	3 (7.3%)	2 (5.1%)
Visual disturbance	3 (7.3%)	1 (2.6%)
Allergic conjunctivitis	0	2 (5.1%)
Keratoconjunctivitis	0	2 (5.1%)
Body as a whole	14 (34.1%)	8 (20.5%)
Infection	8 (19.5%)	6 (15.4%)
Flu syndrome	3 (7.3%)	0
Headache	3 (7.3%)	0
Respiratory	4 (9.8%)	5 (12.8%)
Rhinitis	3 (7.3%)	1 (2.6%)
Cough increased	0	3 (7.7%)

Study 012

The sponsor's *Synopsis* provided the following information:

"Five out of 7 of patients in the cyclosporine group and 2 out of 3 patients in the vehicle group reported adverse events. In the masked phase there were a total of 13 adverse events reported, irrespective of causality, of these 5 were ocular and all were experienced by patients in the cyclosporine group: stinging, burning, allergic conjunctivitis, eye oedema and photophobia. In the open label phase there were 10 adverse events, irrespective of causality, of which 4 were ocular: in the cyclosporine-cyclosporine group, 2 patients reported iritis and 1 patient reported stinging sensation in the eye; in the vehicle-cyclosporine group, 1 patient reported burning sensation in the eye."

Pooled data from the main studies

Pooling of results from the first 6 months of studies 002, 003 and 501 was described in the original application.

The incidence of AEs classified as treatment related in the ITT populations in the first 12 months of studies 002, 003 and 501, is shown in Table 26. Note that the Body System numbers include all patients, whereas PTs are only shown for AEs reported by ≥ 1% of patients in ≥ 1 treatment groups.

Table 26: AEs by Body system, pooled data

	CsA 0.05%	CsA 0.1%	Veh/ CsA 0.1%	
Body System **Preferred Term**	**12 mo** **N = 436**	**12 mo** **N=437**	**6 mo controlled phase (Veh)** **N=442**	**6 mo extension phase (CsA 0.1%)** **N=323**
Overall	127 (29.1)	150 (34.3)	93 (21.0)	44 (13.6)
Body as a Whole	7 (1.6)	8 (1.8)	8 (1.8)	2 (0.6)
Headache				
Cardiovascular		2 (0.5)		
Digestive	4 (0.9)	1 (0.2)	1 (0.2)	1 (0.3)
Metabolic and Nutritional			1 (0.2)	
Musculoskeletal	1 (0.2)			
Nervous	2 (0.5)	4 (0.9)		
Respiratory	3 (0.7)	7 (1.6)	1 (0.2)	1 (0.3)
Skin	3 (0.7)	5 (1.1)	7 (1.6)	
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)
Foreign body sensation	12 (2.8)	8 (1.8)	8 (1.8)	2 (0.6)
Hyperaemia conjunc 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)
Discharge eye	9 (2.1)	4 (0.9)	7 (1.6)	1 (0.3)
Photophobia	9 (2.1)	7 (1.6)	3 (0.7)	
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)
Dry eye	7 (1.6)	2 (0.5)	2 (0.5)	
Epiphora	1 (0.2)	8 (1.8)	3 (0.7)	2 (0.6)
Urogenital		1 (0.2)		

Serious adverse events and deaths

011: 2 deaths (1 from respiratory infection, in a patient on CsA; 1 from renal disease in a patient on Vehicle). Other than these, numbers of patients with SAEs reported were: 7/146 on CsA; 6/144 on vehicle. None was considered related to study drug.

002, 6 month double blind extension: No deaths. Numbers of patients with SAEs reported were: 4/102 on CsA 0.05%; 4/100 on CsA 0.1%; 3/90 on vehicle/CsA 0.1%. None was an

ocular AE and all were considered to have either no relationship to study medication or unlikely to be related to study medication.

003, 6 month double blind extension: No deaths. Numbers of patients with SAEs reported were: 7/125 on CsA 0.05%; 5/114 on CsA 0.1%; 7/121 on vehicle/CsA 0.1%. One was an ocular AE (retinal detachment) and all were considered to have either no relationship to study medication or unlikely to be related to study medication.

501, 18 month double blind extension: 2 deaths (1 from unknown cause in the CsA 0.05% group; 1 from stroke in the Veh/CsA 0.1% group). Other than these, SAEs occurred in 15/112 patients in the Veh/ CsA 0.1% group.

501, initial 6 month study plus 18 month extension: SAEs occurred in 23/143 patients in the CsA 0.05% group and 20/145 patients in the CsA 0.1%. All SAEs were considered to have either no relationship to study medication or unlikely to be related to study medication.

008: 2 deaths, both in the CsA group in the controlled period (both in elderly people with respiratory disease). Other than these, SAEs occurred during the controlled period in 4/122 patients on CsA and 5/118 on Refresh and during the open extension in 12/187 patients. All SAEs were considered not related to study medication.

503: No deaths. SAEs occurred during the controlled period in 3/121 patients on CsA and 3/117 on Refresh, and 0/63 during the open extension. Except for a case of cataract in a patient on CsA, all SAEs were classified unrelated to study medication.

505: No deaths. SAEs occurred in 2/32 patients on CsA and 0/28 on usual treatment. Both events were considered unrelated to the study drug.

005: 4 deaths (myocardial infarction, congestive cardiac failure, breast cancer, lung cancer). Other than these, SAEs occurred in 39/412 patients. SAEs occurring in ≥ 2 patients were: 3 arrhythmia, 3 arthritis, 3 pneumonia, 3 breast carcinoma, 2 accidental injury, 2 CVA, 2 right heart failure, 2 myocardial infarction, 2 thrombophlebitis, 2 cholelithiasis, 2 colitis, 2 gastrointestinal disorder, 2 skin carcinoma. No serious adverse events were classified as related to treatment with CsA.

502: One death (cardiac arrest). Other than these, SAEs occurred in 15/138 patients. None was classified as related to study drug.

006: No deaths. SAEs occurred in 4/127 in the open phase and 3/113 in the controlled phase (2/56 on CsA and 1/57 on Refresh); all considered not related to treatment.

007: No deaths. SAE occurred in 1 patient on lubricant (heart block, considered not related to treatment).

012: No deaths or SAEs.

Specific SAEs

Because of the recognised risk of lymphoma with systemic CsA treatment, lymphoma was specifically sought as an AE with the ophthalmic emulsion. Across all the studies, 7/2310 patients were diagnosed with lymphoma/lymphoma like reaction, all of which were designated unrelated to study treatment. Of these patients, 3 were treated with 0.05% CsA, 3 with 0.1% CsA and 1 with vehicle.

Laboratory findings in clinical efficacy and safety studies

In most studies, standard clinical laboratory data were not collected.

In study 501, clinical laboratory evaluations were performed for serum liver enzymes, creatinine, urea and uric acid at baseline and at months 6, 12, 18 and 24. The variation

among groups shows no meaningful pattern. The trends in the specified parameters over time were also analysed. No one treatment group showed a particular trend regarding the changes in values from low, normal or high and for most patients the values remained within normal limits.

Discontinuation due to adverse events

In study 011, discontinuations occurred in 15/146 patients using CsA 0.05% (burning sensation in eye [5]; eye irritation [3]; infection body as a whole, accidental injury, death, hypertension, gingivitis, somnolence, hypoxia, infection respiratory, pneumonia, herpes zoster, visual disturbance [blurred vision], eye pain, foreign body sensation, photophobia, allergic conjunctivitis, conjunctival hyperaemia, corneal abrasion, corneal ulcer, eye dryness, eye pruritus [1 each]). With the vehicle, 9/144 patients discontinued (visual disturbance [2]; infection body as a whole, rash, eye pain, foreign body sensation, photophobia, irritation eyelid, keratitis, keratoconjunctivitis, superficial punctate keratitis, kidney failure [1 each]).

In the 6 month double blind extension of study 002, discontinuations occurred in 3/102 using CsA 0.05% (burning eye [2]; blepharospasm [1]), 2/100 using CsA 0.1% (burning eye [2] and other AEs) and 3/90 using vehicle/CsA 0.1% (burning eye [3] and other AEs).

In the 6 month double blind extension of study 003, discontinuations occurred in 1/125 using CsA 0.05% (burning eye), 2/114 using CsA 0.1% (burning eye [2] and other AEs) and 10/121 using vehicle/CsA 0.1% (burning eye [6] and other AEs; stinging eye, headache, neoplasm, dyspepsia, sepsis [1 each]).

In the 18 month double blind extension of study 501, discontinuations occurred in 8/143 using CsA 0.05% (burning eye [2] and other AEs; eye irritation eye [1] and other AEs; conjunctival hyperaemia, conjunctivitis, conjunctivitis and other AEs, glaucoma and arthralgia, eye pain and other AEs [1 each]), 2/145 using CsA 0.1% (burning eye, bone fracture and other AEs [1 each]) and 2/112 using vehicle/CsA 0.1% (hyperaemia and eye pain, CVA [1 each]).

In the controlled phase of study 008, discontinuations occurred in 7/122 patients using CsA 0.05% (burning eye [3], eye irritation, pneumonia, stinging eye [2 each], apnoea, bradycardia, conjunctival hyperaemia, death, eye pruritus, eyelid pain, hypotension [1 each]). With the vehicle, 1/118 patients discontinued (corneal ulcer, cough increased [1 each]).

In the open extension of study 008, discontinuations occurred in 23/187 patients using CsA 0.05% (burning eye [6], stinging eye [4], conjunctival hyperaemia [3], eye pain, eye irritation [2 each], accidental injury, allergic conjunctivitis, bone fracture, breast carcinoma, bullous keratopathy, CNS depression, corneal neovascularisation, corneal opacity, general spasm, hypothyroidism, infective conjunctivitis, keratitis, macrocytic anaemia, photophobia, pneumonia, SPK, syncope, visual disturbance, blepharoptosis, carcinoma, conjunctivitis, eye discharge, foreign body sensation, headache, tremor, visual acuity worsened [1 each]).

In the controlled phase of study 503, discontinuations occurred in 7/121 patients using CsA 0.05% (burning eye [2], allergic keratoconjunctivitis, eye pain, eye ulcer, headache, cerebrovascular disorder, nervousness [1 each]). With the vehicle, 6/117 patients discontinued (burning eye [3], eye oedema, inflammation eyelid, rash [1 each]).

In the open extension of study 503, discontinuations occurred in 1/63 patients using CsA 0.05% (AE not specified).

In study 505, discontinuations occurred in 2/32 patients using CsA 0.05% (burning, stinging or irritation of eyes). With usual care, 0/28 patients discontinued.

In study 005, discontinuations occurred in 29/412 patients using CsA 0.1% (burning eye [10], stinging eye [5], conjunctival hyperaemia, cataract, eye pain [3 each], others less common).

In study 502, discontinuations occurred in 6/138 patients using CsA 0.05% (stinging/burning sensation in the eyes [3], conjunctival hyperaemia and eye pain, asthma attack, lymphoma [1 each]).

In the open phase of study 008, discontinuations occurred in 4/127 patients using CsA 0.05% (corneal oedema and SPK, knee replacement, headache and eye pain, eye irritation [1 each]).

In the controlled phase of study 008, discontinuations occurred in one patient using CsA 0.05% (vitreous haemorrhage).

In study 007, discontinuations occurred in 4/41 patients using CsA 0.05% (dry eye, discharge and pain, eyelid irritation, corneal infiltrate, eye irritation [1 each]). With the vehicle, 2/39 patients discontinued (heart block, photophobia, conjunctival hyperaemia, eye pain, foreign body sensation [1 each]).

In the masked phase of study 012, discontinuations occurred in 1/10 using CsA 0.05% (burning, oedema and photophobia).

Postmarketing experience

The sponsor submitted Periodic Safety Update Reports (PSURs) for the calendar years 2005, 2006, 2007 and 2008.

For each year, the number of medically confirmed spontaneous AE reports received is shown in Table 27.

Table 27: Number of medically confirmed AEs by year for Restasis

Year	No. of reports	No. of AEs	No. of reports which included SAEs
2005	122	-	4
2006	117	233	3
2007	61	132	3
2008	118	201	19

SAEs consisted of herpetic keratitis, liver function tests abnormal, refraction disorder (2 cases each), asthenia, aspergillosis, asthma, corneal erosion, corneal oedema, corneal opacity, dacryostenosis acquired, diplopia, dizziness, elevated CPK, epistaxis, Herpes simplex ophthalmic, increased IOP, iris atrophy, keratitis, mouth ulceration, muscular weakness, Mycobacterium avium, optic ischaemic neuropathy, optic neuritis, photopsia, superficial injury of eye and ulcerative keratitis (one case each).

Evaluator's overall conclusions on clinical safety

The new data do not raise any new safety concerns. They contribute additional weight regarding safety to the data contained in the original application, which themselves were

reassuring. The number of patients studied and the duration of studies meet the standards recommended by the TGA-adopted EU guideline (EU 1998).[12]

There was no evidence of systemic toxicity. Ocular AEs related mainly to local irritation and pain, and there was no evidence of sensitisation with increased duration of exposure.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

Regarding the report of the DEWS subcommittee mentioned above, the sponsor should be asked to confirm that the studies described are its own studies 001, 002 and 003.

Clinical Summary and Conclusions

Summary

The additional safety data presented in this application add substantially to those in the original application and provide additional reassurance. However, in the opinion of the evaluator, for the reasons given above, the new subgroup analysis and the additional efficacy data add nothing to the earlier application.

Benefit risk assessment and conclusion

Assessed risk is reduced as a result of this new application. However, as there remains no convincing evidence of efficacy, the benefit risk relationship remains unfavourable. The evaluator recommended against approval.

Regulatory action by other agencies

Health Canada

Based on the recommendations by Health Canada and its Reconsideration Panel, an application was subsequently submitted by Allergan Canada on 13 November 2009. This current application was under review at the time of submission of Allergan Australia's current application and was subsequently approved (see Section I).

The sponsor noted that:

"For this submission, the percentage of patients who responded to treatment was assessed for the primary analysis and the mean change from baseline at 6 months was assessed for the secondary analysis. Responder analyses are clinically meaningful, and provide an endpoint that is much more clinically interpretable than analyses that report change from baseline.

This is because the complete resolution of a given sign or symptom addresses the difficulty in discriminating between the vehicle (that is, 'active' placebo) and test treatment that is often seen in clinical trials of dry eye disease. Recent drug submission meetings with the Therapeutic Products Directorate (TPD) Reviewing Division in Canada and an external Reconsideration Panel convened by the TPD concurred that the use of a responder analysis based on the complete resolution of a given sign or symptom is appropriate for

[12] pp. 121-125 of Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC5A, November 1994. The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions. http://www.tga.gov.au/docs/pdf/euguide/vol3c/3cc5aen.pdf

primary efficacy analyses in clinical studies of patients with dry eye disease. In addition, as the DEWS classification scheme for dry eye disease suggests that the most appropriate target population for Restasis is patients with moderate to moderately severe (Level 2-3) dry eye disease, subgroup analyses of patients with Level 2-3 dry eye disease are to be reported; with subgroup analyses of patients with Level 4 dry eye disease reported for completeness."

Accordingly, during the evaluation of the present application the evaluator obtained from the sponsor documentation of the TPD's position on the matter, in order to place in context the cited text.

V. Pharmacovigilance Findings

Risk Management Plan

Safety Specification

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OPR).

The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 28.

Table 28: Ongoing safety concerns

Important identified risks	None
Important potential risk	None
Important missing information	Paediatric Use Pregnancy and Lactation

The OPR reviewer noted that in the proposed Australian PI, under the Precautions section, it is stated that Restasis has not been studied in patients with recurrent herpes keratitis and also those wearing contact lenses. These safety concerns should be listed under missing information.

Following the inclusion of the above, the above summary was considered acceptable.

Pharmacovigilance Plan

Based upon the clinical trial experience and review of the 6 years of postmarketing data, there are no important identified or potential risks for Restasis. Allergan's pharmacovigilance systems, which include a broad range of signal detection and evaluation methods that are being used to effectively monitor and evaluate the safety of all Allergan products, will be used by Allergan to monitor and evaluate these risks (that is, routine pharmacovigilance).[13]

[13] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The sponsor should include missing safety concerns (patients with recurrent herpes keratitis, patients wearing contact lenses) into the pharmacovigilance action plan.

Risk Minimisation Activities

The sponsor noted that adverse drug reactions which were most commonly reported in clinical studies with Restasis are included in the Adverse Reactions section of the proposed PI for Restasis. Adverse events relating to Restasis have been identified and are well characterised in the Precautions section of the PI and the Consumer Medicine Information (CMI). These sections inform both physician and patient audiences of these possible adverse reactions. To date, these events have not led to any serious outcomes or long term sequelae and are not significant public health concerns. At this time there do not appear to be any safety concerns identified with Restasis that warrant further notification or education to physicians and patients beyond the proposed PI and CMI. Allergan's existing pharmacovigilance activities are robust enough to continue effective monitoring of events of interest as well as detect new and/or significant safety issues should they arise. Based on this, Allergan believed that a routine risk minimisation is acceptable at this time.[14] Allergan will apply any learning from these activities to Restasis through an updated Risk Management Plan or in the PSUR as appropriate.

The OPR reviewer agreed that routine risk minimisation activities were considered sufficient with Restasis.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Restasis is a sterile, oil-in-water emulsion of cyclosporin (0.05% w/w). The ampoules contain 200 µg cyclosporin in 0.4 mL; each drop contains about 27 µL or 13.5 µg cyclosporin.

All chemistry, sterility and quality control questions were resolved and the evaluator recommended registration.

Nonclinical

The evaluator noted that efficacy of cyclosporin in keratoconjunctivitis is suggested by the involvement of cyclosporin in immune and inflammatory pathways of keratoconjunctivitis sicca (KCS). Twice daily administration of the 0.5% strength produced gross improvement in ophthalmic involvement in dogs with KCS. Higher strengths than that proposed for marketing produced greater efficacy.

Higher concentrations also resulted in concentrations of cyclosporin being present in ocular structures in rabbits and dogs, after topical administration. There was no metabolism seen in the eye. Systemic absorption was low in both humans and animals.

Repeat dose toxicity studies (using higher strengths and more frequent dosing) in both rabbits (6 months) and dogs (12 months) showed that cyclosporin was well tolerated. There was slight hyperaemia, signs of discomfort and conjunctival discharge. There was no evidence of systemic toxicity and no treatment related ocular histopathological lesions.

[14] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The sponsor had also submitted previously submitted oral toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies. These were considered to be of limited relevance to topical ocular use as systemic absorption was limited.

The evaluator recommended approval from a nonclinical point of view.

Clinical

Pharmacokinetics

Pharmacokinetics were reviewed in the original application. Cyclosporin 0.05%, 0.1%, 0.2% and 0.4% drops bd were administered in these studies for 12 weeks to 12 months. There was negligible systemic exposure in patients with keratoconjunctivitis sicca.

Efficacy

Dose response study (Study 001)

This is discussed in both clinical evaluation reports (previous submission and current submission). This study used 0.05%, 0.1%, 0.2% and 0.4% vs vehicle in patients with KCS. The primary efficacy variables were Schirmer value without anaesthesia, superficial punctuate keratitis (SPK) and symptoms of dry eye. In relation to the Schirmer value, whilst there was an improvement seen over 12 weeks, no statistically significant difference was seen among the five treatment groups (including vehicle only). There were no statistically significant changes between groups at 12 weeks regarding these endpoints. The evaluator also noted that retrospectively a number of subgroups were defined and analysed. One of these, " preferred Phase III target population" (with at least one eye at baseline with Schirmer ≤ 5mm and SPK (pupil and nasal mean over both eyes) ≥ 1.5 did not show a statistically significant difference between groups.

The evaluator of the current submission concluded that the "optimal dosage has not been properly established" as the formulation used in Study 001 differs from that proposed for marketing. The castor oil content in the formulation used in Study 001 was less than that found in the formulation proposed for marketing. The sponsor claimed that the small changes are irrelevant. In relation to the optimal dose, the sponsor argues that both 0.5% and 0.1% were investigated in the Phase III studies and 0.5% was found to the optimum dose.

Original submission

Study 002 was a multicentre, 6 month double blind randomised study of cyclosporin 0.05% and 0.1% ophthalmic emulsion bd (with six month extension) in patients with moderate to severe KCS.

Efficacy criteria included objective signs of corneal and interpalpebral conjunctival staining, Schirmer test and tear break up time. OSDI scores and other subjective measures were also used.

There was also a responder analysis conducted on the ITT population using values for corneal staining, Schirmer test with anaesthesia, blurred vision and Refresh artificial tears use.

The conjunctival staining results, Schirmer values and OSDI scores were inconsistent and "although reaching statistical significance in some cases, represent biological indeterminate advantages over placebo administration".

Study 003 was also of similar design. There was no statistically significant difference between groups at any of the follow up visits. Similarly, Schirmer's test without anaesthesia showed no significant difference; there was statistically significant difference between active and placebo in relation to Schirmer's test (with anaesthesia). However, this

was small and inconsistent. Other efficacy endpoints (tear break up times and OSDI scores and OSDI score responder analysis) also did not show significant difference.

Study 501 was also a Phase III European multicentre double blind vehicle controlled study of 0.05% and 0.1% bd cyclosporin for up to 2 years. There were no significant difference between actives and placebo at Month 6. Similar results were reported in relation to conjunctival staining, Schirmer values, OSDI scores and facial expression rating scales.

There was a pooled analysis of the three studies. There was a statistically significant difference favouring cyclosporin over vehicle in relation to corneal staining; no difference was seen in relation to Schirmer values or other endpoints. The evaluator of that submission noted that they reconfirm the lack of efficacy of cyclosporin 0.05% eye drops in KCS seen with individual analyses.

The evaluator recommended rejection as "there was minimal or no benefit over and above placebo at most time points". The evaluator also mentioned that the studies showed no "convincing or sustained benefit of 0.05% (0.1%) cyclosporine eye drops vs vehicle, in patients with moderate to severe KS treated up to 6 months, using a range of objective and subjective efficacy criteria".

Current application

This in essence consisted of a reanalysis of studies 002, 003 and 501. Other trial data were also submitted including study 011, a Phase III study. This was not included in the pooled analysis as the severity of KCS was likely to be more severe (that is, those with underlying Sjögren's syndrome, autoimmune connective tissue disease or females ≥ 65 years were the inclusion criteria). These were not relevant to efficacy, as the indications were different.

The reanalysis of previously submitted studies was discussed by the evaluator. The grading system used to identify the subgroups was developed by the Dry Eye Workshop, (DEWS), 2007. The grading system extracted from the evaluation report is shown in Table 14.

Two subpopulations were chosen (that is, patients with Level 2-3 dry eye disease and patients with Level 4 dry eye disease). The efficacy endpoints were also different to those stipulated in the protocol.

These efficacy endpoints were:

- Total corneal and conjunctival staining (score 0-5 for corneal and 0-10 for conjunctival components). Responders were patients with score 0 at 6 months.
- Schirmer tear test with anaesthesia. Responders defined as those with ≥ 10 mm/5 min at 6 months.
- Blurred vision (score 0 = do not have a symptom to 4 = always notice symptom). Responders were patients with score 0 at 6 months.

The pooled analysis showed statistically significant difference of cyclosporin over placebo.

The evaluator's concerns relating to this pooled analysis mainly relate to the following:

1. Justification of subgroup analysis

The DEWS Committee evidence based guidelines recommend the use of cyclosporin for Grade 2-3 dry eye cites the sponsor's studies (002, 003 and 501) as supporting evidence. The evaluator stated that, "to the extent that the committee's opinion was based on the very data which Allergan now seeks to justify re-analysing, the role of the committee must be discounted".

2. The validity of using Grade 2-3

This would be difficult to implement as eligibility criteria in a clinical trial. It is stated that the sponsor asserts that over 60% in each of the studies were DEWS Grade 4. The evaluator was of the opinion that this is based on a loose interpretation of the DEWS classification and is the basis of excluding two thirds of the population from the retrospective analysis. The evaluator questioned the validity of using a different set of eligibility criteria for this retrospective analysis.

Safety

Original submission

In the Phase III studies, most adverse events in relation to ophthalmic cyclosporin were ocular events due to local irritation and there were no significant difference between cyclosporin and vehicle alone. There was no apparent increase in ocular infection or microbiologic abnormality following cyclosporin compared to vehicle.

Current application

There were no new safety concerns. There was no evidence of systemic toxicity. AEs mainly related to local irritation and pain.

Recommendation by the evaluator

The evaluator recommended against approval due to inadequate evidence of efficacy.

Sponsor's response to the Evaluation Report

A detailed response was provided. The sponsor concentrated on four headings as follows.

Validity of the DEWS scheme for classification and management of patients with dry eye disease

The sponsor maintained that the DEWS Committee guidelines were "established by an international group of clinical experts, independently from Allergan, and provided valid, evidence based recommendation for the diagnosis and treatment of dry eye disease". The Committee reiterates that there was no industry influence; the findings of the three studies reflected their experience during the post FDA approval marketing of cyclosporin. This is not a scientific issue *per se* but does not validate the role of the committee.

Rationale for a retrospective subgroup analysis

The evaluator noted that the criteria used in the Phase III clinical trials would have excluded patients with severe dry eye disease; thus, is it feasible from scientific point of view to retrospectively identify and remove patients with severe dry eye disease from the phase III clinical data? The evaluator questions the relevance of using a new classification system to undertake an analysis on subjects who were recruited using different inclusion criteria. The sponsor provided a detailed response in relation to this.

In relation to the validity of using DEWS 2-3 as inclusion criteria in this pooled analysis, the sponsor explained how the inclusion criteria used in the studies could fit into the DEWS classification in relation to Schirmer test score, conjunctival and corneal staining and OSDI score. Table 29, extracted from the sponsor's response, indicates the structure of the DEWS severity classification with regard to Schirmer scores and Table 30, also from the sponsor's response, indicate the structure of the DEWS severity classification with regard to conjunctival and corneal staining.

Table 29: DEWS severity scheme for Schirmer scores

Level	Grade	Criteria
1	Mild	Variable scores
2	Moderate	≤ 10 mm/5 min
3	Moderately severe	≤ 5 mm/5 min
4	Severe	≤ 2 mm/5 min

Abbreviation: DEWS, dry eye workshop.

Table 30: DEWS severity scheme for conjunctival and corneal staining

Level	Grade	Criteria
1	Mild	None to mild
2	Moderate	Variable
3	Moderately severe	Marked central (corneal), moderate to marked (conjunctival)
4	Severe	Severe punctate erosions (corneal), marked conjunctival

Abbreviation: DEWS, dry eye workshop.

Similarly, a further table correlates DEWS severity scheme with symptoms of discomfort.

Thus, the sponsor maintained that Level 2-3 severity could be clearly distinguished from Level 4 from the study population.

Subgroup analysis as proof of efficacy

Subgroup analysis as proof of efficacy was argued on the basis that the studies were all of similar design, heterogeneity of the populations included an improvement in the understanding of dry eye disease since these studies were undertaken. The sponsor stated that Restasis was "more effective than vehicle in the Level 2 to 3 subpopulation in almost all the subanalyses conducted".

The sponsor stated that Grades 2-3 and 4 could be distinguished based on DEWS criteria.

Clarification of the submission history of Restasis in Canada

After rejection notices based on the lack of efficacy, in 2009, there was the submission of similar data set to the current Australian submission following consultation with Health Canada. Approval was granted for the treatment of "moderate to severe (Level 2 to 3) aqueous deficient dry disease, characterised by moderate to moderately severe ocular staining, reduction in tear production and fluctuating visual symptoms, such as blurred vision.

Risk Management Plan

The Risk Management Plan was considered satisfactory.

Risk Benefit Analysis

Delegate Considerations

The original submission, in relation to efficacy, relied on three pivotal studies. The studies were sufficiently similar to include a pooled analysis.

The proposed indication was:

Restasis eye drops are indicated for the treatment of keratoconjunctivitis sicca (chronic dry eye disease) to improve tear production and relieve symptoms in patients whose disease is inadequately controlled by tear substitutes.

The evaluator stated that there was no convincing evidence of efficacy found in the individual or pooled data. Besides, the studies were of short duration (6 months) which is insufficient for the disease modifying effect of cyclosporine to manifest. Longer term (24 months) data were required to assess whether cyclosporin has a sustained effect in this condition.

It was also noted that Allergan supplies Restasis under the Special Access Scheme (SAS). At the time the protocol was negotiated, the sponsor undertook to collect relevant information on its use. *The sponsor should submit the following information in the pre-ACPM response: the total use, the number who require more than six months treatment, the number who are not re-treated either because of inefficacy or adverse events.*

This resubmission essentially contains the same data. However, the indication is amended to reflect *post hoc* subgroup analysis. The proposed indication is:

Topical anti-inflammatory treatment for dry eye disease which is inadequately controlled with artificial tears.

The validity of using *post hoc* analysis to support efficacy of this product is the main issue for consideration by the advisory committee. Whilst this *post hoc* analysis is useful to inform the sponsor on the conduct of a prospective trial: the severity of dry eye disease patients to be recruited etc who are not controlled with artificial tears, the Delegate was of the opinion that it is inadequate to support registration.

Response from Sponsor

The sponsor disagreed with the recommendation of the Delegate that the retrospective analysis is inadequate to support registration of Restasis. Allergan offered the following responses with respect to the issues raised by the Delegate.

Validity of post hoc analysis

Allergan maintained that a retrospective subgroup analysis is appropriate for the support of the efficacy of Restasis and that the criteria used to distinguish between patients with moderate to moderately severe (Level 2-3) and severe (Level 4) dry eye disease were consistent with the DEWS Committee severity grading scheme. Moreover, Allergan maintained that the DEWS severity grading scheme is clinically relevant and allows clinicians to identify patients who would benefit from treatment with Restasis.

Validity of DEWS Committee Recommendations

Subgroup analyses can be justified when the analyses are conducted to answer clinically important questions related to the practical application of treatment (for example, when the benefit differs with the severity of disease) and when the analyses are predefined and well justified.[15] However, a predefined subgroup analysis of patients categorised by severity was not feasible at the time that Allergan's clinical development program was conducted because the definitions of the severity of dry eye disease had not been universally agreed upon and there were no clear recommendations for treatment of dry eye by severity. Since Allergan's clinical development program was conducted, there has been substantial improvement in the understanding of the aetiology of, and recommended treatments for, dry eye disease.[16,17] In addition, the DEWS Committee has since established

[15] Rothwell PM. Lancet 2005; 365: 176-186.
[16] International Dry Eye Workshop (2007). Ocul Surf 2007; 5: 69-70.

a standardised, evidence based rationale for classifying patients with dry eye disease and for stratifying dry eye treatment by severity.[11,18] As highlighted in the response to the evaluator, the DEWS Committee recommendations were established by an international group of clinical experts, with "absolutely no industry influence" as confirmed the Chairman of the DEWS Management and Therapy Committee, and provide valid, evidence based recommendations for the diagnosis and treatment of dry eye disease. The current recommendations from the DEWS Committee for the classification and treatment of dry eye disease are based on a four point severity grading scheme, from mild (Level 1) to severe (Level 4).[17-18] This grading scheme takes into account patient symptoms of discomfort and blurred vision, and clinical signs, including ocular surface integrity, tear film stability, and reflex tear flow.

Clinical Implementation of DEWS Severity Classification

A further criticism by the evaluator was that: "Even if the subgroup analysis had been technically valid, I do not believe the sponsor has identified a subgroup of patients which is well defined and which in practical therapeutics would have enabled clinicians to distinguish patients in whom the product may be expected to be beneficial". The ability of clinicians to accurately grade dry eye severity was studied in a prospective survey of 9 physicians who enrolled 183 patients with dry eye in a nonrandomised, 3 month multicentre study. The conclusions were that a dry eye severity grading scheme for dry eye disease, nearly identical to the DEWS criteria, is simple to implement and results in a greater focus on the treatment of dry eye disease in the earlier stages, when "aggressive, early treatment of tear deficiency might slow or prevent disease progression."[19]

Appropriateness of Methodology of Retrospective Subgroup Analysis

With the introduction of the DEWS severity grading scheme for dry eye disease, Allergan sought to conduct a retrospective analysis of the effect of Restasis in patients using criteria for patients with moderate to severe (Level 2-4) dry eye disease. Despite the limitations of retrospective subgroup analyses, this approach is justified based on the quality of the studies that were conducted, the heterogeneity of the populations in the existing studies, and the improvement in understanding of dry eye disease subsequent to the conduct of these studies. The appropriateness of a retrospective subgroup analysis, and particularly the appropriateness of pooling of studies 002, 003 and 501, was confirmed by a Reconsideration Panel, convened by Health Canada, and by the recommendations from an External Expert Advisory group comprising three Canadian ophthalmologists (corneal specialists) and an epidemiologist. Health Canada considered this approach to be appropriate because the conduct of a new clinical trial in the intended patient population would result in the 'delay in availability of Restasis which, if effective, might compromise patient care". Based on a retrospective analysis of pooled data in the Level 2-3 subpopulation, Health Canada approved Restasis for treatment of moderate to moderately severe aqueous deficient dry eye disease in 2010.

Validity of Results

Findings from the retrospective subgroup analysis showed that Restasis was more effective than vehicle in resolving the signs and symptoms of dry eye disease in patients with moderate to moderately severe (Level 2-3) dry eye disease. Not only were the pooled results significant in the Level 2-3 population but the results in each of the pivotal studies showed clinical benefits across all primary endpoints (with the single exception of blurred

[17] Behrens A, et al. Cornea 2006; 25: 900-907.
[18] Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007; 5: 75-92.
[19] Wilson SE, Stulting RD. Cornea 2007; 26: 284-289.

vision in the 002 study for which the results were similar for the two treatments) with several significant or borderline significant p-values despite the limited sample sizes for the Level 2-3 subgroup.

Given the consistency of the results across all studies in the Level 2-3 subpopulation, the likelihood that the results of the retrospective pooled analysis were generated by chance is remote.

Long Term Clinical Benefit

As indicated by the Delegate, the evaluator from the first submission suggested that the studies included in the submission were of insufficient duration (6 months) for a disease modifying effect of cyclosporin to fully manifest. However, the current submission includes extension phase studies of the 3 pivotal trials, with follow up data for 12 months or more that supports a disease modifying effect of cyclosporin. Although these extension studies did not include a control arm, findings demonstrated continued improvement in signs (corneal staining) and symptoms (OSDI and composite symptoms: dryness, sandy or gritty feeling, burning/stinging, pain, itching, sensitivity to light, and blurred vision) for up to 12 months from baseline.

These findings justify the independent DEWS Committee recommendations that patients with Level 2-3 severity dry eye can be effectively treated with an antiinflammatory such as Restasis and that those with Level 4 severity dry eye disease should include systemic antiinflammatory medication or surgery to treat or prevent sight-threatening corneal complications.**Error! Bookmark not defined.**

Australian Experience with Restasis

The longer term results are also consistent with the experience of Australian ophthalmologists in clinical practice. Expert opinion was provided from two professors of ophthalmology who manage many patients with dry eye disease with Restasis at their tertiary referral centres. Both experts access Restasis for their patients through the SAS and report a clear clinical benefit and need for Restasis. Both ophthalmologists have indicated that Restasis is of most benefit for patients with moderate to severe dry eye disease (Level 2-3) who have failed several treatment regimens before being referred to their centres. One expert stated that: “Restasis is effective in 70% to 80% of patients with moderate to severe dry eye” and that “only patients with the most severe dry eye disease do not respond to Restasis”. Moreover, the experience of practicing ophthalmologists in Australia lends further support to the feasibility of identifying patients with moderate to severe dry eye disease who will benefit from Restasis in clinical practice settings using the DEWS severity grading scheme. This is emphasised in statements from the experts.

Special Access Scheme (SAS)

As requested by the Delegate, the data collected from the SAS for Restasis through to August 2011 was provided as part of the pre-ACPM response.

Overall, the findings provide further support from clinical practice for the favourable safety and tolerability profile of Restasis.

Clinical Risk Benefit of Restasis

The high prevalence of dry eye disease among older Australians is driven, in part, by Australia’s large, ageing population and dry climate.[20,21] Unless more effective treatments are available, the prevalence of dry eye disease among older Australians is expected to

[20] Chia EM, et al. Clin Experiment Ophthalmol 2003; 31: 229-232.
[21] McCarty CA, et al. Ophthalmology 1998; 105: 1114-1119.

increase as the population continues to age. Dry eye disease is a significant public health problem that has a negative impact on patients' daily activities, social and physical functioning, and workplace productivity.[22,23] Individuals with dry eye disease are significantly more likely than unaffected individuals to have difficulty with reading, performing professional work, using computers, watching television, and driving.[24] Moreover, the direct costs of managing patients with dry eye disease and health utilisation costs of these patients is high.[25,26] Of 70 patients with non-Sjögren's syndrome dry eye who were enrolled (before the availability of topical cyclosporin) in a clinical trial, 61% regularly used topical treatments (predominantly artificial tears), more than 40% had undergone punctal occlusion, and 60% had visited a physician at least twice in the past year.[26] Despite these high health utilisation costs, 75% of patients reported that their symptoms had not changed or had worsened during the year before enrolment.[26] These data strongly suggest that new treatments are needed to reduce the substantial impact of dry eye disease on the direct and indirect costs of treatment, and on the negative impact on quality of life and productivity.

The sponsor requested that the Delegate and ACPM give due consideration to the significant burden of dry eye disease in Australia, the favourable risk benefit profile of Restasis, and that currently there are no prescription topical pharmacologic therapies for treatment of patients with moderate to moderately severe dry eye disease (Level 2-3 severity). Restasis is a topical antiinflammatory agent and immunomodulator that is the only therapy available that attempts to treat the underlying mechanisms of dry eye disease. Restasis has an excellent safety profile that has been demonstrated consistently in all clinical studies, including those up to three years duration with 0.1% cyclosporin ophthalmic emulsion.[27] The majority of events reported are local, and of mild to moderate severity. Moreover, clinical trial data show that systemic events are reported at similar rates in Restasis treated and vehicle groups. Cyclosporin 0.1% ophthalmic emulsion administered for 1 to 3 years in clinical studies was safe, well tolerated, and not associated with systemic side effects.[27] Since commercialisation overseas, approximately 12,000 adverse events (AEs) have been reported for Restasis with over 1.1 billion vials distributed globally resulting in an AE reporting rate of 0.1 per 10,000 vials, which is extremely low.

Findings from the retrospective analysis suggest that Restasis benefits patients with moderate to moderately severe dry eye disease (Level 2-3) and based on the additional data contained herein, these benefits increase with continued treatment. Other therapeutic options, such as artificial tears and lubricants only alleviate the symptoms of dry eye disease and generally, are suited to patients with mild dry eye disease. Systemic antiinflammatory medication is reserved for patients with the most severe dry eye disease (Level 4), when other treatment options have proven to be ineffective.**Error! Bookmark not defined.** As such, Restasis fills an unmet medical need in patients with moderate to moderately severe dry eye disease that is effective, has a low treatment burden, and a very low rate of significant adverse events. Given that Restasis shows the greatest benefit in patients with moderate to moderately severe (Level 2-3) dry eye disease, the sponsor suggested an amendment to the indication to stipulate its use in this group of patients. As such the wording of the indication in the proposed Product Information (PI) could be:

[22] Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007; 5: 93-107.
[23] Pflugfelder SC. Am J Manag Care 2008; 14: S102-106.
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Restasis eye drops are indicated for topical anti-inflammatory treatment for patients with moderate to moderately severe dry eye disease (DEWS severity grading scheme, level 2-3), whose dry eye disease is inadequately controlled with artificial tears.

To further emphasise the use in this specific patient group, the sponsor indicated it would also include the following statement in the Dosage and Administration Section of the PI:

The efficacy of Restasis alone has not been demonstrated in patients with more severe dry eye disease (DEWS severity grading scheme, Level 4).

The sponsor also welcomed suggestions from ACPM for the wording of the proposed indication to demonstrate more clearly the specific subgroup of patients that will benefit from the use of Restasis.

Conclusion

The sponsor respectfully disagreed with the Delegate's recommendation to reject this application. Allergan believed that Restasis has been demonstrated to be safe and effective in patients with moderate to moderately severe dry disease (Level 2-3) and should be approved based on the following:

- Dry eye can be a severe, debilitating, and ultimately sight-threatening disease.
- Advances in the diagnosis and management of dry eye disease clearly indicate that inflammation of the ocular surface plays a key role in the pathogenesis of dry eye disease.
- Current treatment options for dry eye disease are palliative, providing symptomatic relief without addressing the underlying mechanisms of the disease.
- Classification and treatment of dry eye disease can be based on a standardised and evidence based four point severity grading scheme, from mild (Level 1) to severe (Level 4), that is applicable in clinical practice.
- Restasis is an antiinflammatory agent and immunomodulator that improves the signs and symptoms of dry eye disease, providing therapeutic benefit. Results from the retrospective subgroup analysis have demonstrated that Restasis is an effective treatment in an identifiable population of patients with moderate to moderately severe dry eye disease and that these benefits increase with continued treatment. For the Level 2-3 subpopulation in the pooled analysis, Restasis treated patients demonstrated statistically significantly greater response to treatment than did vehicle treated patients for all of the primary variables (p . 0.036).
- Clinical experience with Restasis has identified a subgroup of patients with moderate to moderately severe dry eye disease who respond well to treatment and derive substantial clinical benefit. Data across all clinical studies and from post-marketing surveillance since product launch in 2003 in the United States demonstrate that long term treatment has a favourable safety profile and is well tolerated. While the treatment effect over vehicle is not large in this challenging and difficult disease, given the excellent safety profile, the risk benefit assessment of this product is quite positive for its commercial use in patients with moderate to moderately severe dry eye disease.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised that the submission has not satisfactorily demonstrated adequate efficacy in the proposed indication for the following reasons:

Efficacy

The ACPM noted this application was a *post hoc* analysis of data contained in an application which had been previously submitted and, subsequent to evaluation, withdrawn. No relevant new efficacy data were submitted.

The committee was in agreement with the Delegate and evaluator that no convincing evidence of efficacy was found in the individual or pooled data. The studies submitted were of short duration (6 months) which is considered insufficient for the disease modifying effect of cyclosporin to manifest. Longer term (24 months) data are required to assess whether cyclosporin has a sustained effect in this condition. The submission is inadequate in content despite data collected by Cochrane Central Register of Controlled Trials and published prior to this submission.

In the opinion of the committee the proposed indication is too broad. T-cell infiltration of the lacrimal gland should respond to cyclosporin but there has been no theoretical or clinical evidence to support use in the many other causes of this condition, such as rosacea and Sjögren's syndrome.

Safety

No significant safety issues were identified.

The committee expressed concern with the use of *post hoc* analysis on data. The committee were of the understanding that *post hoc* analysis is useful for informing the sponsor on the conduct of a prospective trial but is unable to contribute substantially to a demonstration of efficacy.

Outcome

The application was withdrawn by the sponsor before a decision was made by the TGA.

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Reference/Publication #