A Novel Ocular Formulation of Pimecrolimus for Treatment of Dry Eye

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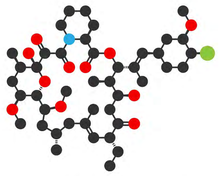
PURPOSE

Symptoms of dry eye disease (DED) are common and often inadequately treated, negatively impacting the quality of life of millions of patients.

There are currently three cyclosporin-based products approved by the FDA for treating dry eye. All three have failed to demonstrate improved control of symptoms vs Vehicle Control in their respective FDA Phase 3 studies.

Pimecrolimus (PMC) is a well-characterized calcineurin inhibitor, which blocks transcription of pro-inflammatory cytokines and belongs to the same pharmacological class as cyclosporin. However, compared with cyclosporin, pimecrolimus has a lower molecular weight, is more lipophilic and exhibits different pharmacokinetic and pharmacodynamic properties.

Figure 1. Pimecrolimus Molecular Structure



PMC is commercially available as a 1% skin cream which was approved by the FDA in 2001 and has been widely used to treat atopic dermatitis.

PMC Suspension **(PMC-S)** is a novel liquid formulation specifically developed for the treatment of ocular inflammation and DED.

Study objective; to assess the safety, efficacy and tolerability of PMC-S as a treatment for DED.

METHOD

A randomized, double-masked, vehicle-controlled, parallel-group, multi-center study consisting of two phases; a 4-week run-in period on Vehicle (b.i.d.) and artificial tears, (Refresh Plus p.r.n.) followed by a 24-week double-masked treatment period (NCT00128245).

Adult subjects meeting the following criteria were eligible:

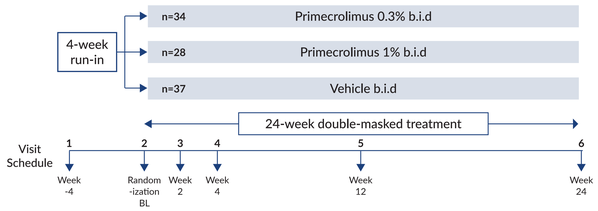
- Use of ocular lubricants for a minimum of 3 months
- Significant signs and symptoms at Visit 1 (Week -4) and Visit 2 (Baseline), in at least one eye
  - Corneal staining score at least 3 on Oxford Grading Scale (0–5)
  - Schirmer's test 7 mm or less/5 min (w/o anesthesia or nasal stimulation)
  - Ocular discomfort score of at least 40 mm on 100 mm VAS Vehicle.

Safety and efficacy assessments were conducted at four follow-up visits.

The primary endpoints were the change from Baseline in corneal fluorescein staining (0–5, Oxford Grading Scale) and ocular discomfort (0–100 mm VAS) at 12 weeks.

A pre-defined sub-group analysis was undertaken for subjects with more severe corneal staining (Baseline score ≥4) and responses to PMC-S were compared with Vehicle Control.

Figure 2. Study Outline



RESULTS

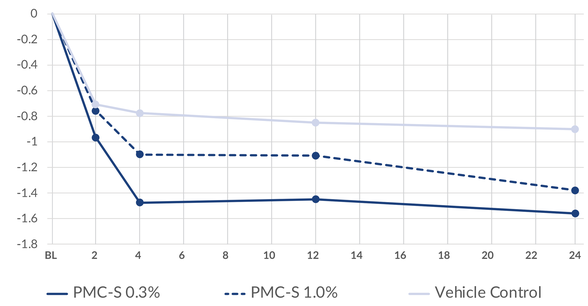
Of 353 subjects, 28% (n=99) fulfilled the pre-defined sub-group criteria and were randomized to treatment with PMC-S 0.3% (n=34), PMC-S 1% (n=28) or Vehicle (n=37).

There was a statistically significant improvement from Baseline in mean scores for corneal staining at Week 12 (p=0.019) and Week 24 (p=0.037) for PMC-S 0.3% vs Vehicle (ITT Population, LOCF).

Table 1. Corneal Staining - Mean Change from Baseline (Weeks 12 & 24)

		PMC-S 0.3% (n=34)	PMC-S 1.0% (n=28)	Vehicle Control (n=37)
	Baseline	4.1	4.2	4.2
WEEK 12 (LOCF)	Change from Baseline (SE)	-1.4 (0.19)	-1.1 (0.22)	-0.8 (0.16)
	Diff in LS Mean vs Vehicle	-0.5485	-0.3046	
	p value	0.019	0.291	
WEEK 24 (LOCF)	Change from Baseline (SE)	-1.6 (0.24)	-1.4 (0.23)	-0.9 (0.19)
	Difference in LS Mean vs Vehicle	-0.7184	-0.4380	
	p value	0.037	0.169	

Figure 3. Corneal Staining – Mean Change from Baseline (ITT Population)

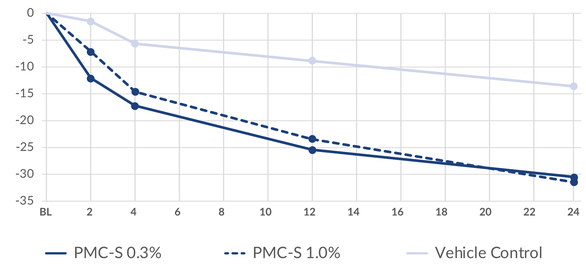


The improvement in ocular discomfort vs Vehicle was statistically significant for PMC-S 0.3% at 12 and 24 weeks (p=0.007 and p=0.012, respectively) and PMC-S 1% at 12 and 24 weeks (p=0.010 and p=0.004, respectively).

Table 2. Ocular Discomfort - Mean Change from Baseline (Weeks 12 & 24)

		PMC-S 0.3% (n=34)	PMC-S 1.0% (n=28)	Vehicle Control (n=37)
	Baseline	67.2	62.0	64.5
WEEK 12 (LOCF)	Change from Baseline (SE)	-25.6 (4.62)	-23.4 (4.64)	-8.8 (4.22)
	Diff in LS Mean vs Vehicle	-15.68	-15.63	
	p value	0.007	0.010	
WEEK 24 (LOCF)	Change from Baseline (SE)	-30.6 (4.78)	-31.6 (3.37)	-13.6 (4.52)
	Difference in LS Mean vs Vehicle	-15.79	-19.01	
	p value	0.012	0.004	

Figure 4. Ocular Discomfort - Mean Change from Baseline (ITT Population)

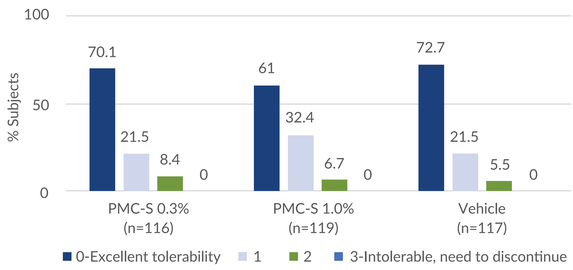


The mean ocular discomfort scores for all treatment arms decreased with successive time points. After 24 weeks, compared with Baseline, mean scores were improved by 45.5%, 51.0% and 21.1% for PMC-S 0.3%, PMC-S 1.0% and Vehicle, respectively. The mean decrease in VAS scores for PMC-S at 24 weeks were 30.6 mm (0.3%) and 31.6 mm (1.0%), compared with 13.6 mm for Vehicle (ITT population, LOCF).

The safety and ocular tolerability findings are presented for the full study population (n=352).

Overall, the safety and ocular tolerability of PMC-S 0.3%, 1% and Vehicle were excellent.

Figure 5. Subject Assessment of Tolerability (12 weeks)



There were no significant safety concerns. None of the most commonly reported AEs in the study were specifically associated with PMC treatment.

Only 12 subjects (3.4%) discontinued study medication due to adverse events during 24 weeks of treatment.

Table 3. Adverse Events & Discontinuations (24 weeks)

	PMC-S 0.3% (n=116)	PMC-S 1.0% (n=119)	Vehicle Control (n=117)
At least one AE	46 (39.7%)	48 (40.3%)	53 (45.3%)
At least one ocular AE	22 (19.0%)	23 (19.3%)	24 (20.5%)
Discontinuations due to AE	3 (2.6%)	5 (4.2%)	4 (3.4%)

CONCLUSIONS/DISCUSSION

In a population of subjects with more severe corneal staining at Baseline, PMC-S 0.3% achieved a statistically significant improvement in the co-primary study endpoint of corneal staining and ocular discomfort at 12 weeks, compared with Vehicle Control. The improvements in ocular symptoms seen with both concentrations of PMC at 12 and 24 weeks, are particularly noteworthy.

PMC-S is very well tolerated, with a safety profile indistinguishable from Vehicle Control.

If these results are reproduced in Phase 3 studies, Pimecrolimus Ophthalmic Suspension has the potential to improve the symptomatic treatment of subjects with DED, in addition to improving ocular surface health.

ABBREVIATIONS
AE, adverse event; b.i.d., twice daily; BL, baseline; DED, dry eye disease; ITT, intention to treat; LOCF, last observation carried forward; LS, least square; PMC, pimecrolimus; PMC-S, pimecrolimus suspension; p.r.n., when necessary; SE, standard error; VAS, visual analog scale; W, week.

DISCLOSURES
Penny Asbell: Commercial Relationship(s); Code C (Consultant/Contractor): Azura, Bausch & Lomb, Centricity, Eyenovia, Glia, Glint, Harrow, Hindi, Horizon, Iolyz, Premark, NEI, Regeneron, Trefoil, Visus; Code R (Recipient): Regeneron, Sylentis, Tear Science; Code C (Consultant/Contractor): Regeneron, Vindico, Visus, Senju, Regeneron | Ian Vessey: Commercial Relationship(s); Code E (Employment): Premark.

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