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Ocular safety and tolerability of high dose PHMB (Polyhexanide) in healthy volunteers

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ODAK Orphan Drug for Acanthamoeba Keratitis

INTRODUCTION AND PURPOSE

***Acanthamoeba* keratitis (AK)** is a rare but severe infectious disease caused by *Acanthamoeba spp.* a ubiquitous free living protozoan. Currently there are no approved drugs for the treatment of *Acanthamoeba* keratitis. The most used compound is **polyhexamethylene biguanide (PHMB)** formulated as ophthalmic solution at a concentration of 0.02% (Oldenburg et al Cornea 2011). Higher concentrations of PHMB may be required for patients with *Acanthamoeba* invading the deep stroma (Pérez-Santonja et al Ophthalmol 2003; Dart Am J Ophthalmol 2009).

In order to evaluate the safety and tolerability of three dose levels (0.04%, 0.06% and 0.08%) **of preservative-free PHMB,** a Phase I study was performed in healthy volunteers. These doses were previously evaluated and found safe in rabbits in a 26-weeks ocular toxicity/tolerability study (**see Poster no. 5171**).
This study is included in the **ODAK** (Orphan Drug for *Acanthamoeba* Keratitis) **project**. This project is funded by the European Commission (European Union Seventh Framework Programme FP7/2007-2013, grant agreement n° 305661) with the aim to let PHMB as the first approved medicinal product for the treatment of *Acanthamoeba* keratitis.
All EU partners of the ODAK Consortium are displayed in the **FIGURE 1**.

FIGURE 1: The ODAK Consortium partners

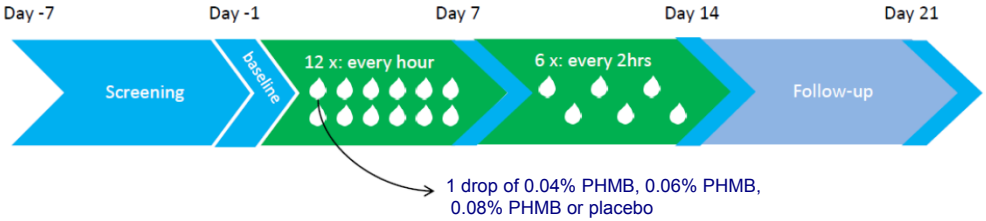
- Società Industria Farmaceutica Italiana (SIFI)-S.p.A. Italy
- University of Rouen, Normandie, France
- Research Toxicology Centre S.p.A., Italy
- Moorfields Eye Hospital NHS, The United Kingdom
- PSR Group B.V., The Netherlands
- Ceratium Limited, The United Kingdom

PATIENTS AND METHODS

This was a double-masked, placebo-controlled, parallel-group multicentre Phase I study (Study code 042/SI). Ninety volunteers (44 M/46 F, age 18-55 years) were randomised to 1 of the 4 study arms: 0.04%, 0.06%, 0.08% PHMB and placebo, in a 3:3:3:1 ratio, respectively. All formulations were **preservative-free**. Subjects were dosed with an **intensive regimen** mimicking that one used during the first month of treatment in patients with *Acanthamoeba* keratitis (**FIGURE 2**). The study was approved by local ethics committees. **Trial registration number: NCT02506257**

Systemic and ophthalmological safety data were recorded. The **primary outcome measure** was the rate of **dose limiting events** (**DLEs**) leading to interruption of dosing. The frequency of **treatment emergent adverse events (TEAEs)** as well as serious AEs (SAEs) starting after the first administration of the study drug were also computed. The rate of occurrence of SAEs, DLEs and TEAEs were compared between groups by Fisher's exact test. Statistical tests were performed 2-sided and with a 5% significance level. A 95% confidence interval for the difference between each respective dose and placebo and p-value was calculated.

FIGURE 2: Dosing schedule



RESULTS

TABLE 1: Subject distribution

	PHMB 0.04%	PHMB 0.06%	PHMB 0.08%	Placebo	Total
Number of subjects					
Treated	26	28	27	9	90
Completed	26(100%)	26(92.9%)	23 (85.2%)	9 (100%)	84 (93.3%)
Withdrawn	0	2 (7.1%)	4 (14.8%)	0	6 (6.7%)

5 = adverse events
1 = protocol non compliance

TABLE 2: Global safety results

	PHMB 0.04%	PHMB 0.06%	PHMB 0.08%	Placebo	Total
Number of subjects	26	28	27	9	90
Any AE	11 (42.3%)	23 (82.1%)	16 (59.3%)	5 (55.6%)	55 (61.1%)
Any SAE	0	0	0	0	0
Any TEAE	**10 (38.5%)**	**22(78.6%)**	**16 (59.3%)**	**5(55.6%)**	**53 (58.9%)**
Any DLE	**0**	**2 (7.1%)**	**3 (11.1%)**	**0**	**5 (5.6%)**

TABLE 3 : Common adverse events (>10%)

	PHMB 0.04%	PHMB 0.06%	PHMB 0.08%	Placebo	Total
Number of subjects	26	28	27	9	90
Conjunctival staining	2 (7.7%)	5 (17.9%)	9 (33.3%)	0	16 (17.8%)
Corneal staining	1 (3.8%)	5 (17.9%)	8 (29.6%)	0	14 (15.6%)
Eye pain after instillation	2 (7.7%)	4 (14.3%)	5 (18.5%)	1 (11.1%)	12 (13.3%)
Conjunctival hyperemia	1 (3.8%)	4 (14.3%)	4 (14.8%)	0	9 (10.0%)

SUMMARY OF RESULTS AND CONCLUSIONS

- **Summary of results**: there were no clinically significant changes in vital signs and laboratory values. Only 5 subjects had events leading to premature withdrawal of treatment (DLEs). No statistically significant differences (Fisher's exact test) were observed between any of the treatment groups.The onset of events occurred shortly (day 0 to 4) after first exposure to treatment and all were resolved between 1 to 15 days. No statistically significant differences in the occurrence of events related to treatments (TEAEs) were observed between groups with the exception of 0.06% PHMB vs. 0.04% PHMB groups (p=0.005, Fisher test, α =0.05).The most common adverse events, reported by ≥10.0% of subjects were conjunctival and corneal staining, eye pain and conjunctival hyperemia.
- **Conclusions**: an intensive regimen with high concentrated PHMB eye drops was safe and quite tolerated in healthy volunteers. According to these data, **0.08% PHMB will be tested in a Phase III study** in patients with *Acanthamoeba* keratitis.

Commercial Relationship Disclosure: V.Papa, E (SIFI SpA); I. J. Van Der Meulen NONE; S. Rottey NONE; G.Sallet NONE; J. Overweel NONE; M.op't Hof NONE; A. Asero, E (SIFI SpA); J.K. Dart NONE.

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