Use of a composite criterion taking into account rescue medication intake in an orphan disease with a seasonal pattern

PSI conference 2017
London, 15th May 2017

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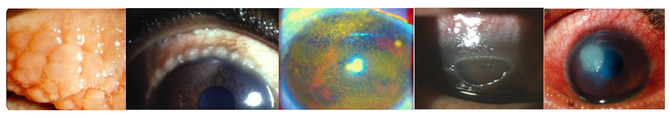
Introduction

A phase III, international, double-masked, vehicle-controlled trial, evaluated the efficacy and tolerability of CsA CE 1mg/ml eye drops for treating active severe vernal keratoconjunctivitis. This study, ended in 2016, was designed to show the superiority of the active drug versus its vehicle, as no reference drug exists in the severe cases of this pediatric disease.

- Prevalence is 3.2/10,000 with a prevalence of VKC with corneal complications of 0.8/10,000 (Bremond-Gignac et al. 2008)
  - A severe and sight-threatening allergic disease
  - Uncommon, recurrent, bilateral chronic inflammation of the ocular surface,
  - seasonal or perennial forms,
  - Children & adolescents; males > females. May resolve by puberty but can persist in adulthood
- Symptoms: Intense itching, tearing, photophobia, mucous discharge, & redness. Corneal involvement leads to a reduced vision
- Signs: corneal involvement
  - Keratitis occurs in up to 50% of cases (Bremond-Gignac et al. 2002) and shield ulcers are sight-threatening complications (Tabbara 1999)
- Consequences: social & educational impacts, poor QoL, impaired vision due to keratopathy
- Complications/impact: Corneal ulceration/perforation, Ocular infections, Impaired quality of life and Impaired vision



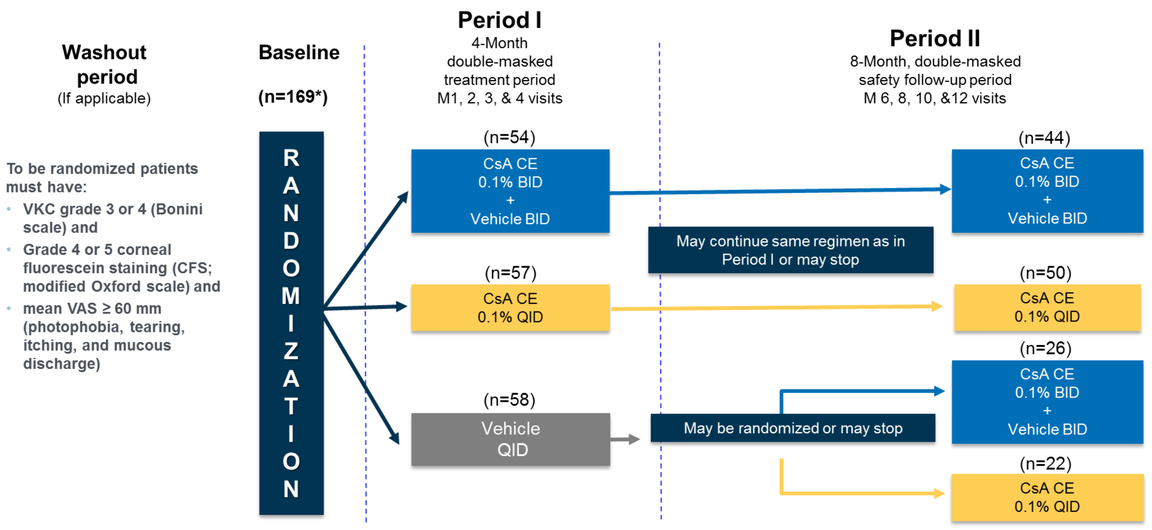
Methodological requirements, discussed with EMA during a Scientific Advice :

- The main endpoint needs to show a continous effect during the allergic season, not only after 4 months
- A rescue therapy is needed for ethic reason but need to be taken into account
- A corticosteroïds-sparing effect study is not possible (no AMM in this indication)
- As a orphan disease, the number of patients needs to be minimized, and several countries around the world have to be included
- The allergic specificity of the disease has to be considered
- Lack of previous data (one phase II, with a reduced number of patients)
- Pediatric population specificity to be addressed (QOL, VAS…)

Requirements from PDCO to be included also.

The proposed composite endpoint was finally endorsed, but as a non validated criterion, the final requirement was that the 3 components of the composite endpoint evolved in the same way and that responders analyses were added to confirm the clinical relevance. Weights of components were challenged and clinically motivated.

Figure 1. Study Design and Patient Disposition



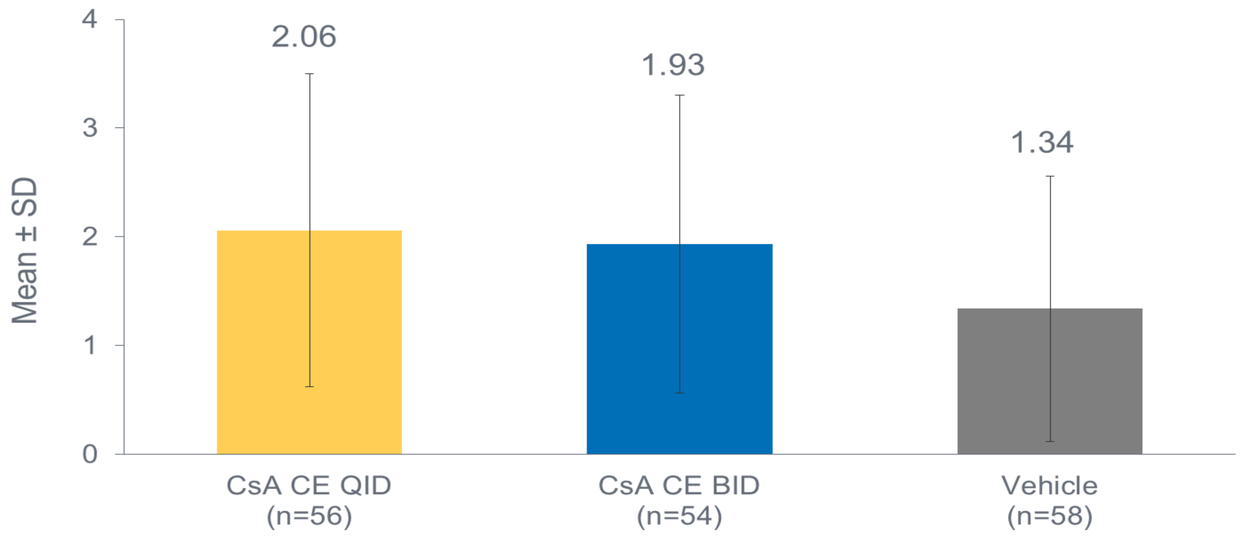
*n = 101 recruited in Europe. BID, twice per day; QID, 4 times per day; CsA CE, ciclosporin A 0.1% (1 mg/mL) cationic emulsion; VAS, visual analogue score; VKC, vernal keratoconjunctivitis.

The primary endpoint was a mean composite score that reflected corneal fluorescein staining (CFS) as assessed by the modified Oxford scale (a 0 to 5 likert scale), need for rescue medication, and occurrence of corneal ulceration during 4 months. The composite score at 4 months was defined as the mean of the 4 efficacy scores taken at each monthly visit, calculated using the following formula:

Patient's score at Month X = CFS (Baseline) – CFS (Month X) + penalty(ies)

Penalty for use of rescue medication: -1 (per course, with a maximum of 2 courses between 2 scheduled visits)
Penalty for corneal ulceration: -1 (per occurrence)

Figure 2. Average Penalties-Adjusted CFS Score Over 4 Months



The composite primary endpoint showed superiority of active treatment over vehicle over 4 months; difference in the least-squares (LS) mean vs vehicle for the high-dose group (0.76; 95% CI, 0.26-1.27; p = 0.007) and the low-dose group (0.67; 95% CI, 0.16-1.18; p = 0.010). Results shown in **Figure 2**.

Table 1. Contributions of the 3 Primary Endpoint Components to the Overall Treatment Effect

Component	Parameter	CsA CE QID vs Vehicle	CsA CE BID vs Vehicle
Mean change from Baseline of the CFS score per month	LS Mean (absolute contribution)	0,523	0,528
	Adjusted p-value	0,014	0,014
	Relative contribution (%)	70.3 %	77.6 %
Mean number of rescue medication courses per month	LS Mean (absolute contribution)	0,220	0,149
	Adjusted p-value	0,010	0,055
	Relative contribution (%)	29.6 %	21.9 %
Mean number of ulcer occurrences per month	LS Mean (absolute contribution)	0,001	0,003
	Adjusted p-value	0,966	0,966
	Relative contribution (%)	0.1 %	0.5 %

Mean change from Baseline of the mean CFS score per month = CFS score over 4 months; mean number of rescue medication courses per month = total number of rescue courses over 4 month/number of visits; mean number of ulcer occurrences per month = total number of ulcer occurrences during the 4 months/number of visits. BID, twice per day; CFS, corneal fluorescein staining; CsA CE, ciclosporin A 0.1% (1 mg/mL) cationic emulsion; FAS, full analysis set; LS, least-squared; QID, 4 times per day.

The treatment effect for the primary endpoint was mainly driven by CFS score with more than 70% of the effect (**Table 1**).
A majority of the CsA CE patients did not need rescue medication during the 4-month randomized treatment period. The proportions of patients with at least one course of rescue medication were 32.1%, 31.5%, and 53.4% in the CsA CE QID, CsA CE BID, and vehicle groups, respectively.For the mean number of ulcer occurrences per month, no statistical difference was found vs. the vehicle.

Conclusions

During the initial, 4-month randomized treatment phase patients who received active doses showed significant improvement in signs of VKC vs. patients receiving vehicle alone. The proposed composite endpoint allowed to show the overall benefit of the drug, in a case where a rescue drug-sparing effect was not ethical.

Disclosures

M. Deniaud has been a consultant for Santen (C)
B. Scherrer has been a consultant for Santen (C)
M. Amrane and D. Ismail are employed by Santen SAS (E)
C = Consultant; E = Employee; N = No commercial relationship