1. BACKGROUND AND RATIONALE

Allergy is an over-reaction of the body’s immune system to harmless foreign substances or allergens. Allergic conjunctivitis (AC) affects 16 to 20% of the general population (Pitt et al., 2004). AC is characterized by ocular itching, redness, chemosis, eyelid swelling, and watery discharge from the eyes and nasal passages.

The pathophysiology of AC can be divided into an “early phase” and a “late phase”. In the early phase, exposure to allergen induces an immunoglobulin E (IgE)-mediated reaction involving mast cells. The mast cells degranulate and release pre-existing inflammatory mediators (mainly histamine), which are primarily responsible for the early phase symptoms. The late-phase response begins 4–6 hours after release of the mast cell mediators. The response is characterized by T-lymphocyte activation and infiltration of the conjunctiva by inflammatory cells (Bacon et al, 2000). In many patients, repeated acute exposure and response to allergy-causing agents lead to a persistent late phase inflammatory reaction (Choi et al, 2008). In its more persistent form, AC constitutes a complex ocular surface disease involving many mechanisms (Baudouin, 2007).

Mild AC can be treated with anti-histamine (anti-H1)/vasoconstrictor agents or mast cells stabilizers (MCS). Additional measures include artificial tears, cool compresses, oral anti-histamine agents (anti-H1), and allergen avoidance (AAO, 2011). However, in some patients, the symptoms are not adequately controlled by these options, especially where
repeated acute exposure to allergens—such as dust mites—induces a persistent inflammatory reaction (Baudouin, 2007). For these patients, topical corticosteroids can be added to their treatment regimen in accordance with current therapeutic guidelines that recommend the use of steroids for patients with AC who are not satisfactorily treated with anti-histamine agents/mast cell stabilizers (anti-H1/MCS). Given the risk of increased ocular pressure (IOP) and/or cataract formation with steroids, the lowest dosage and frequency of administration is preferred.

The distinct mechanisms of action of cyclosporine A (CsA) and prednisolone acetate (PA) provide a relevant rationale for developing a fixed-dose combination (FDC).

- Glucocorticoids, such as PA, are particularly effective in blocking most inflammatory pathways in allergic reactions, especially those of late-phase mediators that perpetuate the persistent and chronic forms of ocular allergy (Bielory, 2008).
- Cyclosporine A, a calcineurin inhibitor, is a potent but selective immuno-modulating agent that has been identified as a potentially effective drug for AC due to its ability to inhibit the early phase reaction in AC (Sperr et al, 1997; Whitcup et al, 1996) by the suppression of mast cell degranulation (Shii et al, 2009). Also, CsA was shown to strongly suppress certain ocular symptoms in late phase and delayed-type reactions in AC models (Shii et al, 2010). CsA is also effective in controlling ocular allergic inflammation by blocking Th2-lymphocytes proliferation and IL-2 production (Kari et al, 2010).

Combining CsA with PA is expected to control inflammation associated with AC in an additive, or even synergistic manner. Therefore, the anticipated efficacy of such a FDC would be comparable to a high dose concentration of steroid. From a safety perspective, the combination would allow the cumulative total dose of PA necessary to achieve efficacy in AC to be limited, therefore potentially reducing the corticosteroid side effects. In addition, the use of low doses of both CsA and PA would ensure a better local tolerability whilst achieving sufficient efficacy to control symptoms in AC, and hence achieve a better compliance than co-administration of separate products.

2. MARKET

The AC market is worth $1.1 billion worldwide (2011) and is dominated by the US. Most of the value in the US market today is in Rx anti-H1/MCS, with olopatadine (Patanol®, Pataday®) as a clear leader followed by more than 10 other products, including the recent launches (Bepreve® 2009 , Lastacaft® 2011).

In the US, the steroids market is largely dominated by loteprednol (Lotemax®, Alrex®), which represents more than 90% of prescription steroids.

The treatment armamentarium does not fully satisfy the market, with an identified need for effective treatments for patients who are not satisfactorily treated with anti-H1/MCS, as well as a need for better-tolerated products than high dose steroids, due to side-effects (e.g., increased IOP and/or cataract formation).

The CsA and PA combination would be the first prescription FDC in the treatment of AC.
3. OCULAR FORMULATION, PHARMACOKINETICS & CLINICAL STUDIES

Formulation
FOV1101 suspension eye drops are a sterile, preserved FDC of PA 0.12% w/v and CsA 0.02% w/v in a buffered aqueous vehicle. The product is intended for topical ophthalmic administration, and is supplied in multi-dose dropper bottles. The FOV1101 formulation employs excipients which are commonly used in currently marketed ophthalmic products, including the preservative benzalkonium chloride at a concentration of 0.01%.

Preclinical pharmacokinetic (PK) studies
Sanofi-Fovea has conducted a total of four preclinical PK studies, using CsA alone or with both components, given as FDC (FOV1101) or in co-administration. The studies showed that PA was rapidly metabolized to prednisolone in vivo, and that both CsA and prednisolone were found in the target tissues (conjunctiva and cornea) at levels which increased with dose and over time, whilst plasma exposure was general below limit of quantification. Further, the PK profiles of PA, prednisolone and CsA were comparable for the FDC and co-administration in the target tissues, and independent of the individual components.

Clinical studies
Sanofi-Fovea conducted a proof-of-concept trial (08-003-27; NCT00833495) in 2009 using co-administered CsA and PA. This prospective, multicenter, randomized, double-blind, placebo-controlled study with 150 patients was conducted in the USA utilizing Ora’s Enviro-CAC™ clinical technology. The co-administration of low doses of CsA and PA was compared to PredForte® alone or vehicle alone during a 2-week dosing period. Co-administration of CsA and PA had the same efficacy and a better safety profile (no increase in IOP) than PredForte®, a prescription drug with an 8-fold higher dose of PA, in patients treated for the signs and symptoms (itching and redness) of persistent ocular allergic inflammation (non responding to 1-week pre-treatment with Pataday®).

Sanofi-Fovea also conducted, in 2010, a prospective randomized, double-blind placebo-controlled Phase 2b trial (10-003-03; NCT01120132). The purpose of this study was to determine the efficacy and safety of the administration of CsA and PA compared to placebo in the treatment of allergic conjunctivitis, using diary and office assessments of various ocular and nasal allergy signs and symptoms. This 28-day study enrolled 716 patients in the US.

This clinical data package provided key information to design the Phase 3 program that will be conducted with the FDC product.

4. OCULAR SAFETY PROFILE

For each active substance of the FDC, CsA and PA, there is extensive nonclinical and clinical safety information available in the literature. The toxicity of CsA has been widely studied during the development of various pharmaceutical forms for the treatment of systemic or ophthalmic diseases, whilst that of prednisolone (the active metabolite of PA) is described in published studies. Summaries of the main findings can be found in the prescribing information, labels and/or NDA pharmacology reviews of Sandimmune® and Restasis® for CsA, and in the prescribing information for Orapred ODT® and Pred Forte® for PA.

For both active substances of the FDC that are given by ocular instillation, the systemic levels of exposure are estimated to be several hundred-fold lower than the levels encountered after
oral or parenteral administration. Specifically, blood CsA levels are >600-fold higher in organ transplant patients than for dry eye patients given eye drops of Restasis® 0.05% emulsion (which is 2.5 times more concentrated in CsA than FOV1101), and prednisolone plasma levels have been predicted to be >400-fold higher for patients taking a 30-mg oral dose than for those to be treated with FOV1101.

Sanofi-Fovea has conducted a series of local tolerance/toxicity studies of the topical formulation in rabbits, either with the combination of CsA and PA, or with CsA alone. From these nonclinical studies and in particular a 6-week safety rabbit study performed with topical ocular administration of CsA and/or PA compared to vehicle, no overt local or systemic toxicity effects are to be expected in patients treated with FOV1101 eyedrops QID for up to 6 weeks due to the low dose levels of the drug substances given locally and the subsequent low systemic exposures.

5. VALUE PROPOSITION

FOV1101, through its dual mode of action, represents a new potentially safe therapeutic option for AC patients who cannot be relieved from their persistent inflammation with current available treatment. In addition, the use of low doses of both CsA and PA would ensure a better local tolerability while achieving sufficient efficacy to control symptoms in AC, and hence achieve a better compliance than co-administration of separate products.

6. REFERENCES


6. CONTACTS

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