

# Development of tivanisiran, a topical siRNA designed to treat dry eye disease

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## Introduction

Dry eye is disease (DED) emerges as a new prevalent ocular affection in modern-day, affecting between 5 to 50% of the population worldwide [1]. DED is defined a multifactorial disease of the ocular surface that combines alterations of the tear film, inflammatory processes and neurosensory abnormalities [2]. While the main sign of DED is the appearance of corneal damage, symptoms generally manifest as ocular pain/discomfort, dryness, itching and burning. Management of DED primarily relies on artificial tear substitute use, although other strategies such as autologous serum, punctal occlusion, lid hygiene and dietary changes are common [3]. In the United States, only two prescription drugs have been approved for the treatment of DED: a cyclosporine ophthalmic emulsion (also approved in Europe) and lifitegrast [4,5]. These non-steroidal anti-inflammatory agents only present efficacy in a subset of patients. There is thus a significant unmet need for effective treatments that will improve signs and symptoms of DED.

## Tivanisiran's mechanism of action

Sylentis is developing tivanisiran (former SYL1001), a novel small interfering RNA (siRNA) aimed at treating DED. Tivanisiran is a non-modified, 19-base pair, oligonucleotide sodium salt specifically designed to silence the Transient Receptor Potential Cation channel subfamily V member 1 (TRPV1) mRNA. Transient silencing occurs via the RNA interference (RNAi) mechanism of action in which the siRNA is required to reach the cytoplasm where it can bind to complementary TRPV1 mRNA [6,7]. This produces a degradation of the mRNA, preventing its translation into protein. TRPV1 is expressed in primary afferent nociceptive neurons of the peripheral nervous system, in the central nervous system and in non-neuronal tissues such as the skin, epithelial airway and different eye tissues [8,9]. The cornea is densely innervated by sensory afferent fibers of the trigeminal nerve, where TRPV1 acts as nociceptive transducer for the sensing and transmission of pain stimuli [10]. In corneal epithelial cells, the receptor can be implicated in inflammatory and fibrogenesis processes, as well as regulation of response to stress [11]. Since none of the commercially available treatment target the pain pathway, TRPV1 appears as an attractive and innovative target for the treatment of this disease.

## *In vitro* and *in vivo* studies for tivanisiran

Non-clinical studies of tivanisiran have been previously described in more details [12]. Briefly, *in vitro* transfection of tivanisiran was shown to produce a 50-60% decrease in TRPV1 mRNA levels. High specificity was reported: the compound acts specifically on TRPV1 rather than other members of the TRPV family or other sequence-related receptors, minimizing the risk of toxicity. Corroborating this observation,

tivanisiran did not affect cell viability. Interestingly, biodistribution studies after single topical instillation of tivanisiran in New Zealand rabbits demonstrated that the compound efficiently reached corneal and conjunctival tissues five and 30 min after administration. Of note, intracellular siRNAs are rapidly phosphorylated on their 5' P, allowing differential quantification of the compound (phosphorylated and non-phosphorylated forms). In these studies, the highest amount of tivanisiran was detected in response to the dose of 1.125%.

Non-clinical pharmacokinetic studies were conducted in two species after topical administration of tivanisiran (at doses up to six times the clinical dose) during 28 consecutive days. Analysis revealed that the compound was below the Lower Limit of Quantification (LLOQ) at all tested time-points and in response to all dose-levels in all plasma and systemic tissues, suggesting minimal systemic absorption. In these animals, tivanisiran did not produce any apparent alterations in clinical signs or ophthalmologic exams. Most importantly, corneal sensitivity, as assessed by esthesiometer, confirmed that the compound is devoid of anesthetic effect. Overall, these observations indicate that tivanisiran displays a good local and systemic tolerability.

## Clinical studies for tivanisiran

Safety and efficacy of tivanisiran have been evaluated in three clinical trials [13]. Tivanisiran sodium salt ophthalmic solution was formulated in absence of preservative at pH 7.2 at five nominal concentrations: 3.75 mg/mL (0.375%), 7.5 mg/mL (0.75%), 11.25 mg/mL (1.125%), 15 mg/mL (1.5%) and 22.5 mg/mL (2.25%). In the phase I study (EudraCT No: 2010-023113-56, NCT01438281), thirty healthy volunteers received single or multiple administrations of tivanisiran for seven consecutive days, with the counter-lateral eye used as control. No related adverse events (AEs) were reported and no clinically significant changes were observed for ocular and physical examinations. Tivanisiran could not be detected in any of the plasma samples collected regardless of the time-points (LLOQ<10 ng/mL).

Thereafter, two phase II trials, named SYL1001\_II and SYL1001\_III (EudraCT No: 2012-001177-93, NCT01776658 and EudraCT No 2014-004857-15, NCT02455999) were conducted in a total of 126 patients with mild to moderate DED [13]. Each trial tested two different doses of tivanisiran that were compared with placebo (approximately 20 patients per arm). Tivanisiran was instilled once a day during 10 consecutive

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days. The trials met the primary endpoint of identifying the most efficient dose in reducing signs and symptoms of DED. Tivanisiran 1.125% decreased the scoring on the visual analogue scale (VAS) for ocular pain as compared with placebo. Differences were statistically significant from Day 4 and were maintained until the end of treatment. Following this short time treatment-period, no changes were detected in the Ocular Surface Disease Index (OSDI). Signs of DED were also affected in these trials. A significant percentage of patients showed improvement in conjunctival hyperemia after 10 days of instillation with tivanisiran 1.125% and 0.75% compared with placebo. Similar findings were made for corneal fluorescein staining (CFS), although difference did not reach statistical significance. Tear break up time (TBUT) was prolonged of two seconds at Day 10 of treatment with tivanisiran 1.125% respective to baseline. As previously reported, the incidence of AE was similar between tivanisiran-treated groups and placebo. Overall, these trials suggest a good safety profile for tivanisiran and the dose of 1.125% was selected for future trials.

### Current trial for tivanisiran

HELIX study (EudraCT No: 2016-003903-79, NCT03108664) is ongoing to assess the effect of tivanisiran 1.125% in 300 patients with moderate to severe DED. The trial is being conducted in six different countries, involving more than 39 sites. Primary endpoints are change from baseline in VAS for ocular discomfort/pain, CFS and conjunctival hyperemia. Confirmation of efficacy will allow to determine whether tivanisiran would be beneficial for these patients and may satisfy the unmet needs of DED.

### Conflict of Interest

AMB, VR, VG TM, BV and AIJ are employed by Sylentis.

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