Orally Absorbable Rebamipide Prodrug (SA001) for Prevention and Therapy of Dry Eye Syndrome

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**Purpose**
The aim of the present study was to provide an orally absorbable rebamipide prodrug (SA001) for prevention and therapy of dry eye syndrome, which can overcome the low oral bioavailability of rebamipide.

**Methods**
Rebamipide and SA001 were orally administered at 100 mg/kg and 130 mg/kg (about 100 mg/kg as rebamipide) in SD rats, respectively, and rebamipide concentration in blood samples taken from the rats were monitored using UPLC-MS. To evaluate the therapeutic effect of SA001, dry eye rat models were induced by intramuscular injection of scopolamine hydrobromide with exposure to an air draft and were divided into normal, negative control (NC), 2% rebamipide eye-drop, and oral SA001 (10, 20 mg/kg) groups (n=4 rats per group). Tear secretion and fluorescein cornea staining were measured on the 10th day after treatment. Also mRNA levels of secretory mucin (MUC2 and MUC5AC), TNF-α, and Interleukin (IL-1β and IL-6) in eye tissue were determined by qRT-PCR and amount of transmembrane mucin (MUC1 and MUC16) in conjunctiva was measured by western blotting.

**Results**
SA001 showed 8.9 times higher AUC and 26.8 times higher Cmax values than those of rebamipide after oral administration in rats. In dry eye rat models, SA001 increased tear volume and reduced National Eye Institute (NEI) score by cornea staining down to less than 2, resulting in significantly decreased ocular surface damage. SA001 demonstrated enhancement of secretory mucin (MUC2 and MUC5AC) mRNA expression and decrease of inflammatory cytokine (TNF-α, IL-1β, and IL-6) mRNA expression related with anti-inflammatory effect. According to western blotting, SA001 also induced the synthesis of transmembrane mucin (MUC1 and MUC16) proteins compared to NC and 2% rebamipide eye-drop.

**Conclusion**
SA001 is a rebamipide prodrug which has higher oral bioavailability compared to poorly absorbed rebamipide. In dry eye rat model, oral SA001 improved tear production and ocular surface shape as well as increased secretory and transmembrane mucin in eye tissue. These results suggest that SA001 is a prominent candidate of the first orally available drug for the treatment of dry eye syndrome, which can also supply the improved patient compliance overcoming eye-irritation and inconvenience of the eye drop products.