INTRODUCTION

There is a substantial evidence associating presence of excessive adenosine in the anterior chamber of eye with the development of ocular hypertension [1,2]. Although it is well known that A3 adenosine receptor (A3AR) antagonist inhibits chloride channels in the non-pigmented epithelial cells and decreases the aqueous humor production, their specific effect in modulation of trabecular meshwork outflow as well as inhibition of the aqueous humor production. The safety and efficacy of FM101, together with its suitability for oral administration, indicates that it has potential as a candidate drug for the treatment of glaucoma.

MATERIALS AND METHODS

Properties of FM101
- Small molecule/nucleoside derivative
- Molecular weight: 432.12
- High oral bioavailability
- Half life: 3.5–5 hours (species dependent)

Pharmacokinetics: PK profile of FM101 was evaluated in male ICR mouse, SD rat and Beagle dog following oral (10 mg/kg) and intravenous (2 mg/kg) administration.

Efficacy: FM101 was orally administrated to mice with dexamethasone-induced intraocular pressure (IOP) elevation. IOP was measured at 4 h following oral administration of FM101. Expressions of fibrosis markers were analyzed by immunostaining, immunoblot and RT-PCR.

Safety: The potential toxicity of FM101 was evaluated in Sprague-Dawley rats by single and 2-week repeated dose toxicity studies. It was also evaluated in Beagle dogs following 10-day repeated administration. In addition, genetic toxicity and safety pharmacology studies were conducted.

CONCLUSION

FM101 markedly reduced IOP by remodeling of trabecular meshwork which increases outflow of aqueous humor. Moreover, our data demonstrate that FM101 has excellent pharmacokinetic and safety profiles by oral administration. Together, these results indicate that FM101 could be a novel target and first-in-class candidate for glaucoma.

RESULTS

Fig 1. Plasma concentration in male rats

Table 1. PK parameters in male rats

- Parameters: IV, PO, IP
- Dose: 1 mg/kg, 2 mg/kg, 5 mg/kg
- PK: Cmax, Tmax, AUC0-24h, Vd, t1/2

Fig 2. Lowering of IOP in normal rabbits

Fig 3. Lowering IOP in normal rabbits and DBA/2J glaucoma model mice.

Fig 4. Lowering IOP in glucocorticoid-induced glaucoma mice model via oral administration

Fig 5. Inhibition of gene and protein expression of fibronectin, smooth muscle actin and myosin and regulation of MMP & TIMP in trabecular meshwork by oral administration.

Table 3. Summary of Non-clinical safety studies

- Safety pharmacology
- Respiratory System: no adverse effects (75, 150 & 300 mg/kg)
- Cardiovascular System (Telemetry): no adverse effects (75, 150 & 300 mg/kg)

- General toxicology
- Single dose toxicity study (Rat): MTD > 2,000 mg/kg
- 1-week repeated dose finding study (Rat): NOAEL > 1000 mg/kg/day

- Genetic toxicology
- In vitro Mammalian Chromosomal Alteration Test: Negative

REFERENCE

1. Braun JS. Ecto-5'-nucleotidase-positive cells in the choroid and ciliary body of the rat eye. Anat Rec (Hoboken) 2010;293:379-82