Drug-drug interaction between TAS-303 and simvastatin/midazolam in healthy subjects

Yuji Kumagai¹, Tomoe Fujita², Masako Aso¹, Hideki Amano¹, Yoshinobu Sasaki¹, Masaki Kawai³, Toru Takenaka⁴, Makoto Nagaoka³, Koichiro Hoashi³

¹Clinical Trial Center, Kitasato University Hospital, Japan, ²Department of Pharmacology and Toxicology, Dokkyo Medical University School of Medicine, Japan, ³Clinical Development II, TAIHO PHARMACEUTICAL CO., LTD., Japan, ⁴Pharmacokinetics Research Laboratories, TAIHO PHARMACEUTICAL CO., LTD., Japan

Background: TAS-303, a selective noradrenaline reuptake inhibitor, is currently at the stage of Phase II development for stress urinary incontinence in Japan. In nonclinical study, TAS-303 has a time-dependent inhibitory potential toward Cytochrome P450 (CYP) 3A. In order to evaluate the effect of TAS-303 on CYP3A activity and the safety of TAS-303 administered in combination with simvastatin/midazolam, we conducted a clinical trial in healthy adult subjects (n=12).

Methods: The major objective is to investigate the effect of TAS-303 3 mg on activity of CYP3A by evaluating the pharmacokinetics (PK) of simvastatin at an oral dose of 5 mg and midazolam at an intravenous dose of 1 mg. Simvastatin and midazolam are sensitive substrates susceptible to PK drug interactions with CYP3A. This study was a single-centre, open-label, single-group study. Procedures of this study are shown in Figure 1. The point estimates for the geometric mean ratio for the PK parameters of simvastatin/midazolam and their 90% CIs in the presence and absence of TAS-303 were calculated.

Results: The point estimates (90% CIs) for the geometric mean ratio for the Cmax and AUC0-t of simvastatin were 1.326 (1.089 to 1.615) and 1.420 (1.041 to 1.938) respectively. The point estimates (90% CIs) for the geometric mean ratio for the C0 and AUC0-t of midazolam were 1.088 (0.935 to 1.265) and 1.090 (1.030 to 1.154) respectively.

Adverse events were headache (1 subject) and diarrhoea (1 subject) in the simvastatin monotherapy period; and paraesthesia (1 subject) and diarrhoea (1 subject) in the TAS-303 plus simvastatin combination period; and somnolence (8 subjects), vertigo (1 subject), and monoparesis (1 subject) in the midazolam monotherapy period; and insomnia (1 subject) and somnolence (12 subjects) in the TAS-303 plus midazolam combination period.

Conclusions: These study results indicated that TAS-303 3 mg was a weak inhibitor of CYP3A in the small intestine, but was no effect on CYP3A in the liver. In addition, no safety-significant interaction in combination with simvastatin/midazolam was observed. These results showed that there were no tolerability concerns on TAS-303 in combination with simvastatin/midazolam.