blinded placebo-controlled study. Participants received single oral tablet of DA-8159 (12.5 to 300 mg) or placebo. Adverse effects and pharmacokinetic parameters were monitored during experiments. DA-8159 was well tolerated and the frequency of adverse events was dose-related. The most common side effects were headache and facial flushing, which are related with inhibition of PDE5. Mean plasma concentrations of DA-8159, maximum concentration (Cmax), and area under the concentration-time curve from time 0 to the time of the last detectable concentration (AUCo–tldc) increased with increasing dose, with the time to the peak concentration in plasma occurring at 1.17 to 1.92 hours postdosing. Plasma elimination half-life (t1/2) ranged from 7.3 to 12.1 hours with an average of 10 hours. This study indicates DA-8159 is safe and well tolerated after single oral dose in healthy males up to 300 mg without severe adverse events and warrants further clinical investigation.

[PA1–21] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C]

Evaluation of electroretinogram and retinal histopathology in rabbits administered DA-8159, a selective PDE 5 inhibitor

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DA-8159, a selective inhibitor of phosphodiesterase type 5 (PDE5: IC50 5ng/ml), is being developed as a new treatment for erectile dysfunction. Since DA-8159 has been shown to inhibit PDE6 enzyme (IC50 53ng/ml), we evaluated the effect of DA-8159 on electroretinogram (ERG) and retinal histopathology in rabbits. The effect of oral DA-8159 (5 to 30mg/kg) on ERG recordings was investigated at pre-treatment, 1 and 5 hrs after administration in rabbits. Plasma and intravitreal concentration of DA-8159 was determined at each time point, and the electromicroscopic examination on retinal blood vessel was also performed. DA-8159 did not induce any significant difference in either a- or b-wave amplitudes. The implicit time of the a- and b-wave also did not show remarkable changes. In the highest dose group, however, mild and transient changes in rod and cone response were observed 1 hr after administration, which disappeared at 5 hrs post-dosing. Intravitreal concentration of DA-8159 was about half of the concentration of sildenafil after the same oral dose. There was no histopathological evidence of toxicity on retinal blood vessels. These data suggest DA-8159 has a lower risk potential of ocular side effects, but further evaluation of the effects of DA-8159 on visual functions in human must be performed.

[PA1–22] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C]

Induction of penile erection in spinal cord-injured rabbits by administration of DA-8159, a new selective PDE 5 inhibitor

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DA-8159 is a new, highly selective, potent cyclic-GMP phosphodiesterase 5 inhibitor developed by Dong-A Pharmaceutical Company(Kyunggi, Korea) as an oral drug for the treatment of erectile dysfunction. NO- cGMP signal transduction pathway plays a key role for relaxation of corpus cavernosal smooth muscle. In this study, the efficacy of DA-8159 was evaluated by measuring the length of uncovered penile mucosa in spinal cord injury(SCI) rabbits. Spinal cord injury is regarded as one of the main risk factors for erectile dysfunction in human. In this study, SCI was induced by spinal cord transection at the local level(L2–L4) preventing the effective release of penile neurotransmitter, nitric oxide, from nonadrenergic–noncholinergic nerves. It was proven that penile erection was