Case study: Non clinical study outcomes of Fasiglifam discontinued prior to approval
– Consideration from non-clinical toxicity study results

○ 福井 英夫

Axcelead Drug Discovery Partners 株式会社 非臨床安全性研究

○ Hideo FUKUI

Nonclinical Safety Research, Axcelead Drug Discovery Partners, Inc.

GPR40 is highly and dominantly expressed in pancreatic beta cells and is activated by medium- to long-chain free fatty acids (FFAs) to potentiate glucose stimulated insulin secretion. Fasiglifam was a novel, oral, and selective small molecule agonist of GPR40 under development as a once-daily treatment for type 2 diabetes. Unfortunately, a development program was terminated late in phase III clinical trials due to liver safety concerns. Three important serious liver injury cases were identified among around 9100 patients treated with Fasiglifam; one case was adjudicated to be a clear Hy’s Law case [ALT or AST > 3 x ULN (upper limit of normal) and total bilirubin > 2 x ULN] and the two remaining cases were considered to closely approximate Hy’s Law cases. Fasiglifam-related liver toxicity was also observed in repeat-dose dog toxicity studies. It was characterized by elevation of plasma AST, ALT, ALP, and/or bilirubin and portal/peripoortal granulomatous inflammation with crystal formation in histopathology. This toxicity was observed in a 4-week study at 1000 mg/kg/day.

The toxicity measures were greater than those observed at 150 and 80 mg/kg/day in 13- and 39-week studies, respectively, indicating that the toxicity was both dose- and duration-dependent. We analyzed the composition of foreign body materials observed in dog liver and identified Fasiglifam and Fasiglifam glucuronide. Although elevations of serum bilirubin and ALT were observed in repeat-dose rat studies, no histopathological changes indicative of liver injury were observed in any rat studies even at the lethal dose of 2000 mg/kg/day. In this symposium, the mechanisms for liver toxicity of Fasiglifam in dogs, safety margins in plasma and bile, human relevancy and discussion with FDA and PMDA would be introduced.