Development of anti-fibrotic drug for primary biliary cholangitis

Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease in which the cause of failure of autoimmune by unknown mechanism is involved in the pathogenesis. Due to cholestasis, hepatic parenchymal cell destruction and fibrosis occur, eventually leading to liver failure from cirrhosis. Ursodeoxycholic acid (UDCA) has an anti-inflammatory effect and is administered from the beginning, but no effect is observed in advanced state. Asymptomatic PBC has a very good prognosis as long as it remains asymptomatic PBC, but about 10 to 40% (about 25% over 5 years) transfers to symptomatic PBC. In the state of advanced decompensated cirrhosis, there is no remedy (anti-fibrotic drug) for liver cirrhosis in the current therapeutic treatment. PRISM Pharma found PRI-724, a low-molecular compound that can selectively inhibit the protein interaction between β-catenin and CREB-binding protein. We examined the anti-fibrotic effect of PRI-724 using HCV induced liver fibrosis mice, and as a result, remarkable improvement was observed concerned to liver fibrosis in the treated group as compared with the control group. Based on the results of this pre-clinical study, we started a doctor-initiated clinical trial (phase I test) to verify the safety and tolerability of PRI-724 for patients with HCV cirrhosis in August 2014, Investigational drugs were administered to patients. After administration of PRI-724, several cases of C-P class B patients showed improvement in liver function, and a fibrosis area was decreased from liver histology examination. Improvement from C-P class B to A, which is considered irreversible in the current treatment, was observed in several administration cases. In this research proposal development plan, in pre-clinical study of PRI-724 using PBC mouse model in 2018, we will obtain the result of pharmacological pharmacology test. In April 2019, after analyzing the anti-fibrotic treatment effect in detail, we consulted with PMDA in advance, and confirmed the study protocol of the doctor-initiated clinical trial by receiving face-to-face advice until November, 2019. We aim to accomplish this research by preparing IRB application materials and submitting clinical trial reports at the implementation facility by February - March, 2020. If it keeps going smoothly, patient registration will start from April, 2020 and Phase I test will be carried out. With the results of this research proposal, if the development of an effective therapeutic agent for cirrhosis caused by PBC is realized, various complications accompanying liver cirrhosis are improved, not only to rescue decompensated cirrhosis patients without treatment, it is expected to contribute economically.