AB083. TEW-7197, a novel orally bioavailable activin receptor-like kinase 5 inhibitor, promotes regression of fibrotic plaque in a rat model of Peyronie's disease

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Background: To examine therapeutic effect of TEW-7197, a novel small molecule inhibitor of activin receptor-like kinase 5 (ALK5), in an animal model of Peyronie's disease (PD) and to determine mechanisms by which TEW-7197 ameliorates fibrotic responses in primary fibroblasts derived from human PD plaque.

Methods: Rats were distributed into 3 groups (N=6 per group): age-matched controls without treatment; PD rats receiving vehicle; and PD rats receiving TEW-7197 (10 mg/kg). PD-like plaque was induced by repeated intratunical injections of 100 µL of each of human fibrin and thrombin solutions on days 0 and 5. TEW-7197 was given orally five times a week for 2 weeks. On day 30, erectile function was measured during the electrical stimulation of the cavernous nerve, and the penis was then harvested for histologic examination. Fibroblasts isolated from human PD plaque were used to determine anti-fibrotic effects of TEW-7197 *in vitro*.

Results: TEW-7197 induced significant regression of fibrotic plaque in PD rats *in vivo* through reduced infiltration of inflammatory cells and reduced expression of phospho-Smad2, which resulted in a recovery of erectile function. TEW-7197 also abrogated TGF-β1-induced enhancement in extracellular matrix production and hydroxyproline content in PD fibroblast *in vitro* by blocking TGF-β1-induced phosphorylation and nuclear translocation of Smad2 and Smad3, and by inhibiting TGF-β1-induced transdifferentiation of fibroblasts into myofibroblasts.

Conclusions: In view of the critical role of TGF-β and Smad pathway in the pathogenesis of PD, antagonizing this pathway through the use of ALK5 inhibitor may represent a novel targeted therapy for PD.

Keywords: Peyronie's disease (PD); transforming growth factor-beta (TGF-β); activin receptor-like kinase 5 (ALK5); TEW-7197

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