Toxicokinetics and Immunogenicity of CBX129801, a Pegylated C-Peptide Drug for Type 1 Diabetes Replacement Therapy, in Sprague Dawley Rats

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Abstract

Purpose To assess toxicokinetics (TK) and immunogenicity of CBX129801 in rats in a 4-week subcutaneous (SC) dosing study with 4-week recovery period.

Methods Two groups of rats were injected with saline or CBX129801 (80 mg/kg/week) on Days 0, 7, 14, 21, and 28 followed by 28-day recovery. For TK study, blood samples were collected at predetermined times after the first and last dose. CBX129801 plasma concentrations were determined using a validated ELISA assay. TK was determined by standard model-independent methods. Immunogenicity was tested for plasma on Days 28 and 56 using a validated bridging immunoassay.

Conclusion Following SC injection of CBX129801 at 80 mg/kg/week in rats, T1/2 did not change due to repeated doses. CLss/F values were 122 mL/day/kg in males and 65.6 mL/day/kg in females. Associated Vdss/F values were 234 mL/kg in males and 85.5 mL/kg/kg in females. AUC was 12,100–17,000 nM•day in males and 12,200–25,000 nM•day in females. AUCmax values were 4,530 and 7,050 nM and AUCinf values were 17,000 and 23,700 nM•day in males and females, respectively. AUC was approximately equal to the first dose (Table 1 and Figure 2). The exposure in females was higher than that in males (Table 1).

TK Analysis

CBX129801 T1/2 values ranged from 2.00 to 3.30 days in both sexes and did not change due to repeated doses (Table 1 and Figure 1). T1/2 values were 2.53 and 2.73 days in males and females, respectively. AUC was 12,100–17,000 nM•day in males and females, respectively. AUCmax was 4,530 and 7,050 nM and AUCinf was 17,000 and 23,700 nM•day in males and females, respectively. AUC was approximately equal to the first dose (Table 1 and Figure 2). The exposure in females was higher than that in males (Table 1). CBX129801 did not accumulate following repeated dosing and its TK exposure after repeated dosing was approximately equal to the first dose (Table 1 and Figure 2). During recovery, the plasma concentrations of CBX129801 decreased over time and there was no detectable drug at the end of the recovery period in both sexes (Day 56) (Figure 3).

Immunogenicity Analysis

All screened Day 29 and Day 56 samples yielded values below the run specific cut point and were reported as ADA-negative. Samples yielded screen ADA-negative results regardless of dose and gender designation (Figures 4 and 5).

Conclusions CBX129801 exhibited no accumulation following 5 weekly subcutaneous doses. CBX129801 T1/2 and AUC did not change due to repeated weekly doses. Exposure in females was higher than that in males. Exposure gradually decreased following cessation of dosing to undetectable levels at the end of recovery in both sexes. The lack of antibodies against CBX129801 in both sexes suggests that CBX129801 is not immunogenic.