Abstract

Purpose
To evaluate the maternal toxicokinetics and fetal exposures of CBX129801 in studies which assessed the development toxicity, after subcutaneous injection for it does to pregnant female rats and rabbits.

Methods
CBX129801 was administered to five groups of pregnant rats and rabbits by subcutaneous injection of 3, 10, 30, or 100 mg/kg/dose for a total of 4 subdoses from Gestation Day (GD) 6 to GD 17 in rats and from GD 1 to GD 21 in rabbits. Maternal and fetal blood samples were collected at predetermined times. Plasma was assayed for CBX129801 by validated ELISA assays. Toxicokinetic parameters were determined by model independent methods.

Results
Following first or repeated subcutaneous injections of CBX129801, \( T_{\text{max}} \) values in rats ranged from 0.250 to 2.00 days and in rabbits from 1.00 to 2.00 days, \( Cl/F \) values ranged from 0.837 to 1.00 day in rats and the mean apparent \( T_{1/2} \) did not change due to repeated dosing in both species. CBX129801 C

Introduction

Type 1 diabetes is characterized by the body's inability to produce proinsulin and consequently both insulin and C-peptide.

Objective
It is estimated that millions people in the U.S. and Europe have type 1 diabetes and about 15,000 children are diagnosed with type 1 diabetes in the U.S. each year.

C-peptide is a reliable marker of 

Methods

Study Design
Five groups of pregnant rats and rabbits received a total of 4 subdoses of CBX129801, namely 3, 10, 30, or 100 mg/kg/dose from Gestation Day (GD) 6 to GD 17 in rats and from GD 1 to GD 21 in rabbits at 3, 10, 30, or 100 mg/kg/dose. Maternal and fetal blood samples were collected at predetermined times. Plasma was assayed for CBX129801 by validated ELISA assays. Toxicokinetic parameters were determined by model independent methods.

TK Analysis

Figure 1
Mean CBX129801 Plasma Concentration-Time Profiles in Pregnant Rats Following Repeated Subcutaneous Injection of CBX129801 in an Embryofetal Developmental Study (GD 5, GD 9, GD 13 and GD 17) Linear Scale

Figure 2
CBX129801 C

Figure 3
Mean CBX129801 Plasma Concentration-Time Profiles in Pregnant Rats Following Repeated Subcutaneous Injection of CBX129801 in an Embryofetal Developmental Study Linear Scale

Figure 4
Mean CBX129801 C

References

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Conclusions
The exposure of CBX129801, as measured by \( C_{\text{max}} \) and \( AUC_{(0-4)} \), increased in a dose proportional manner after single or repeated dosing in both species.

Results
CBX129801 was readily measurable in plasma of both species with \( T_{\text{max}} \) values ranging from 0.250 to 2.00 days in rats and from 1.00 to 2.00 days in rabbits (Tables 1 and 2 and Figures 1 and 2).

In rats, CBX129801 \( C_{\text{max}} \) values following the first dose were 261, 997, 2946, and 9868 nM/g, and \( AUC_{(0-8)} \) values were 548, 1850, 5300, and 21000 ng/mL/day for CBX129801 doses of 3, 10, 30, or 100 mg/kg, respectively (Table 1). In rabbits, mean CBX129801 \( C_{\text{max}} \) values following the first dose were 359, 1205, 3630, and 10000 ng/mL/g, and mean \( AUC_{(0-4)} \) values were 1055, 2705, 5110, and 17500 ng/mL/day for CBX129801 Doses of 3, 10, 30, or 100 mg/kg (Table 2).

CBX129801 TK exposure (\( C_{\text{max}} \)) was dose proportional in both species (Table 1 and Figure 1) after single or repeated dosing. Half-life ranged from 0.27 to 1.89 days in rats and from 2.14 to 2.30 days in rabbits. Repeated dosing resulted in no accumulation in rats and 1.36- to 1.66-x accumulation in rabbits. The fetal exposure was minimal in both species.

Conclusions

Table 1
Summary of TK Parameters of CBX129801 in Pregnant Rats Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/fetal Developmental Study (GD 5, GD 9, GD 13 and GD 17)

Table 2
Summary of TK Parameters of CBX129801 in Pregnant Rabbits Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/fetal Developmental Study (GD 6, GD 11, GD 16 and GD 21)