T2367

Toxicokinetics of CBX129801, a Bio-active C-peptide for Potential Replacement Therapy in Type 1 Diabetic Peripheral Neuropathy, Following Subcutaneous Injection of CBX129801 in Rats in a 6-Month Study with a 7-Week Recovery Period

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ABSTRACT

Purpose:

To assess the toxicokinetics (TK) of CBX129801 in Sprague Dawley Rats following once weekly subcutaneous injection for 26 doses.

Methods:

Four groups received subcutaneous injections of CBX129801 at 0, 3, 10 and 30 mg/kg/week for 26 doses. Blood samples were collected on Days 0, 84 and 175 at predose and 24, 48, 72 and 168 hours postdose. Additional predose samples were collected on Days 28, 56, 119 and 147 and single time-point samples were collected during the recovery period on Days 182, 196, 210 and 224. The plasma was assayed for CBX129801 by a validated ELISA assay. TK parameters were determined by model-independent methods.

Results:

Following the first subcutaneous injection of CBX129801 at 0, 3, 10 and 30 mg/kg, C_{max} values were 25, 721 and 1330 nM in males and 270, 973 and 1970 nM in females, respectively. Corresponding AUC_{tau} values were 781, 2580 and 5250 nM·day in males and 920, 3060 and 8160 nM·day in females. Apparent $T_{1/2}$ values were similar between gender and dose groups and ranged from 1.25 to 1.85 days.

The repeated doses resulted in comparable exposure to that following the first dose in both sexes. The exposure following the first or repeated doses increased as a function of CBX129801 doses in a dose-proportional manner in both sexes. Male rats exhibited slightly lower exposure than females in all groups following the first dose (~15-36%) and repeated doses (~10-60%). CBX129801 appeared to achieve a steady state on Day 28 and was maintained through the last dose administration to Day 175. Plasma concentrations decreased over time following the last dose and were below the assay quantification limit of 0.213 nM by the end of the 7-week recovery period.

Conclusions:

Upon subcutaneous administration to rats, CBX129801 exposure was dose proportional and had a linear TK. Repeated dosing resulted in no CBX129801 accumulation.

Purpose

To evaluate the TK of CBX129801 in rats and monkeys following single and repeated subcutaneous dosing of CBX129801.

Introduction

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

It is estimated that 4 million 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.

Scientific data suggest that C-peptide deficiency in type 1 diabetes is a contributing cause of many of the long-term complications associated with this disease, despite insulin replacement therapy.

A protective effect of C-peptide replacement therapy was demonstrated in preclinical and early clinical studies; however, native C-peptide has a half life of ~60 min.

Cebix is developing CBX129801 (PEGylated synthetic human C-peptide) for the treatment of long-term complications of diabetes (e.g., peripheral neuropathy, nephropathy).

This work presents the TK of CBX129801 in rats and monkeys following single and repeated subcutaneous dosing.

Methods

Study Design

Four groups of rats received subcutaneous injections of CBX129801 at 0, 3, 10 and 30 mg/kg/week for 26 doses. Blood samples were collected on Days 0, 84 and 175 at predose and 24, 48, 72 and 168 hours postdose. Additional predose samples were collected on Days 28, 56, 119 and 147 and single time-point samples were collected during the recovery period on Days 182, 196, 210 and 224.

Analytical Method

The plasma was assayed for CBX129801 by a validated ELISA assay.

TK Analysis

The TK parameters were determined by standard model independent methods (Gibaldi and Perrier, 1982) using Phoenix WinNonlin Professional Version 6.1 (Pharsight Corp., Mountain View, CA).

Figure 1

Mean Plasma Concentrations of CBX129801 in Rats Following Subcutaneous Injections of CBX129801 in a 3/6-Month Toxicity Study

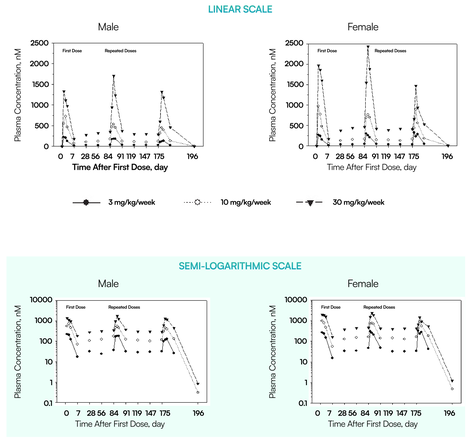

Figure 2

CBX129801 C_{max} versus CBX129801 Dose in Rats Following Subcutaneous Injections of CBX129801 in a 3/6-Month Toxicity Study

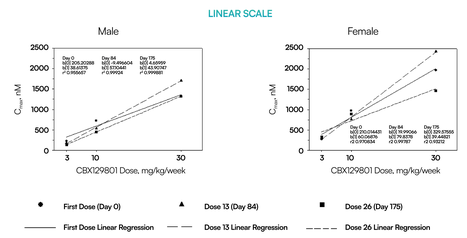

Figure 3

CBX129801 AUC_{tau} versus CBX129801 Dose in Rats Following Subcutaneous Injections of CBX129801 in a 3/6-Month Toxicity Study

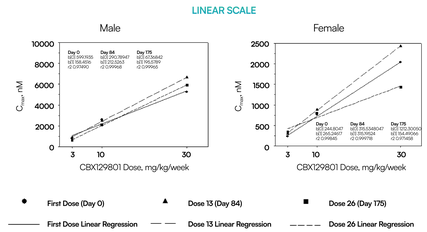

Table 1

Summary of CBX129801 Toxicokinetic Parameters in Rats Following Subcutaneous Injections of CBX129801 in a 3/6-Month Toxicity Study

Parameter	Dose, mg/kg/week					
	Male			Female		
	3	10	30	3	10	30
Day 0 (Dose 1)						
C_{max}, nM	225	721	1,330	270	973	1,970
T_{max}, day	1.00	2.00	1.00	1.00	1.00	1.00
$T_{1/2}$, day	1.40	ND	1.85	1.25	1.31	1.36
AUC_{tau}, nM·day	781	2,580	5,250	920	3,060	8,160
AUC_{inf}, nM·day	816	ND	5,750	948	3,160	8,490
C_{max} M/F Ratio	0.833	0.741	0.675	-	-	-
AUC_{tau} M/F Ratio	0.849	0.843	0.643	-	-	-
Day 84 (Dose 13)						
C_{max}, nM	180	537	1,710	302	761	2,430
T_{max}, day	2.00	2.00	2.00	1.00	2.00	2.00
$T_{1/2}$, day	ND	ND	ND	2.01	ND	ND
AUC_{tau}, nM·day	881	2,480	6,650	1,200	3,550	9,750
C_{max} M/F Ratio	0.596	0.706	0.704	-	-	-
AUC_{tau} M/F Ratio	0.734	0.699	0.682	-	-	-
Day 84/0 C_{max} Ratio	0.800	0.745	1.29	1.12	0.782	1.23
Day 84/0 AUC_{tau} Ratio	1.13	0.961	1.27	1.30	1.16	1.19
Day 175 (Dose 26)						
C_{max}, nM	131	451	1,320	325	890	1,470
T_{max}, day	3.00	2.00	2.00	1.00	2.00	2.00
$T_{1/2}$, day	ND	1.70	1.67	1.83	1.73	1.80
AUC_{tau}, nM·day	612	2,080	5,920	1,370	3,170	5,740
C_{max} M/F Ratio	0.403	0.507	0.898	-	-	-
AUC_{tau} M/F Ratio	0.447	0.656	1.03	-	-	-
Day 175/0 C_{max} Ratio	0.582	0.626	0.992	1.20	0.915	0.746
Day 175/0 AUC_{tau} Ratio	0.784	0.806	1.13	1.49	1.04	0.703

ND - Not Determined

Results

CBX129801 was readily measurable in rat plasma with T_{max} values ranging from 1.00 to 3.00 days (Table 1 and Figure 1).

CBX129801 C_{max} values following the first dose were 25, 721 and 1330 nM in males and 270, 973 and 1970 nM in females for CBX129801 doses of 0, 3, 10 and 30 mg/kg, respectively. Corresponding AUC_{tau} values were 781, 2580 and 5250 nM·day in males and 920, 3060 and 8160 nM·day in females (Table 1).

The TK exposure following repeated doses was approximately equal to that following the first dose (Tables 1 and 2).

CBX129801 $T_{1/2}$ values were similar between gender and doses and ranged from 1.25 to 2.01 days (Table 1).

Male rats exhibited slightly lower exposure than females in all groups following the first dose (~15-36%) and repeated doses (~10-60%).

The exposure following the first or repeated doses increased as a function of CBX129801 doses in a dose-proportional manner in both sexes (Table 1 and Figures 1, 2 and 3).

CBX129801 appeared to achieve a steady state on Day 28 and was maintained through the last dose administration to Day 175.

Plasma concentrations decreased over time following the last dose and were below the assay quantification limit of 0.213 nM by the end of the 7-week recovery period.

Conclusions

Upon subcutaneous administration to rats, CBX129801 exposure was dose proportional and had a linear TK. Repeated dosing resulted in no CBX129801 accumulation.

References

Gibaldi, M. and Perrier, D., 1982. Pharmacokinetics, Second Edition, Marcel Dekker, Inc., New York.

Acknowledgments

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