W5426

Toxicokinetics of CBX129801, a Bio-active C-Peptide for Potential Replacement Therapy in Type 1 Diabetic Neuropathy, in Rats and Monkeys After Subcutaneous Injections

A. Kousba[1], S. Barrack[2], D. Naas[3], M. Mazzoni[3];

[1]BioAgilytix, San Diego, CA, 92121. [2]Cebix Incorporated, La Jolla, CA, 92037. [3]ProDev Consulting Services, Ltd., Poway, CA, 92064.

BioAgilytix

ABSTRACT

Purpose:

To assess the toxicokinetics (TK) of CBX129801 in rats and monkeys following once weekly subcutaneous injection for 5 doses.

Methods:

In Sprague-Dawley rats, five groups received subcutaneous injection of CBX129801 at 0, 2.74, 8.22, 27.4 or 80 mg/kg/week for 5 doses, respectively, and recovery groups were dosed at 0, 27.4 and 80 mg/kg/week. In cynomolgus monkeys, toxicology groups were dosed with 0, 1.33, 4.0 or 13.3 mg/kg/week and recovery groups were dosed with 0, 4.0 or 13.3 mg/kg/week. In monkey, the toxicology and recovery groups were combined for TK analysis. Blood samples were collected at predetermined times and plasma was assayed for CBX129801 by a validated ELISA assay. TK was determined by model independent methods.

Results:

Following the first injection of CBX129801 to rats at 1.74, 8.22, 27.4 and 80 mg/kg, C_{max} values were 156, 440, 1540 and 4530 nM in males and 412, 564, 2210 and 7050 nM in females, respectively.

Corresponding AUC_{inf} were 539, 1690, 4950 and 18100 nM•day in males and 1060, 2190, 8050 and 24700 nM•day in females. Apparent $T_{1/2}$ values ranged from 1.26 to 1.62 days. In monkeys, mean C_{max} values were 250, 881 and 2780 nM in males and 252, 877 and 2400 nM in females for doses of 1.33, 4.0 and 13.3 mg/kg, respectively. Corresponding mean AUC_{inf} were 1920, 5570 and 17700 nM•day in males and 1800, 5410 and 14400 nM•day in females. Apparent mean $T_{1/2}$ values in monkeys ranged from 2.63 to 4.67 days. In both species, CBX129801 TK exposure increased as a function of CBX129801 doses and achieved a steady state on Days 14 to 21. CBX129801 exposure in female rats was higher than males but displayed no apparent genderrelated differences in monkeys. CBX129801 plasma concentrations at the end of the recovery period were either undetectable or substantially low. CBX129801 did not accumulate in rats and displayed slight accumulation in monkeys following repeated doses.

Conclusions:

Upon subcutaneous administration to rats and monkeys, CBX129801 exposure appeared to be dose proportional and suggested a linear TK. Repeated dosing resulted in no CBX129801 accumulation in rats and slight accumulation in monkeys.

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.

Materials and Methods

A. Study

Rats received subcutaneous injection of CBX129801 once every week at 0, 2.74, 8.22, 27.4 and 80 mg/kg/week for 5 doses. Recovery groups received CBX129801 at 0, 27.4 and 80 mg/kg/week for 5 doses.

Monkeys received subcutaneous injection of CBX129801 once every week at 0, 1.33, 4 and 13.3 mg/kg/week for 5 doses. Recovery groups received CBX129801 at 0, 4 and 13.3 mg/kg/week for 5 doses. Data for the toxicology and recovery groups were combined for analysis in monkeys.

Blood samples were collected from rats and monkeys as follows: On Day 0, at 6 hours postdose and then on Days 1, 2, 3, 4, 5 and 6. Predose samples were collected on Days 7, 14 and 21. On Day 28, blood was collected prior to dosing and at 6 hours postdose and then on Days 29, 30, 31, 32, 33 and 34. During the recovery period, blood was collected from rats on Days 35, 42, 49 and 56 and from monkeys on Days 37, 42, 49 and 56.

B. Analytical Method

AC220 was administered at doses ranging from 12 to 450 mg for 14 days followed by a 14-day rest in each 28-day cycle (Intermittent Dosing, ID). Two groups of subjects received AC220 for 28 days at 200 and 300 mg doses (Continuous Dosing, CD).

C. TK Analysis

The TK parameters were determined by standard model independent methods (Gibaldi and Perrier, 1982) using WinNonlin Professional 5.2.1 (Pharsight Corp., Mountain View, CA). The dose-normalized trough plasma concentrations were utilized for statistical analysis assessment of steady-state using ANOVA with a p value set at ≤ 0.05 (GraphPad Prism v 5.01, GraphPad Inc., CA).

Results

CBX129801 was readily measurable in plasma of both species with T_{max} values ranging from 1.00 to 3.00 days (Tables 1 and 2 and Figures 1 and 4).

CBX129801 C_{max} values following the first dose in rats were 156, 440 and 1540 nM in males and 412, 564 and 2210 nM in females for CBX129801 doses of 2.74, 8.22 and 27.4 mg/kg, respectively. Corresponding AUC_{inf} were 539, 1690 and 4950 nM•day in males and 1060, 2190 and 8050 nM•day in females (Table 1).

In monkeys, mean CBX129801 C_{max} values were 250, 881 and 2780 nM in males and 252, 877 and 2400 nM in females for CBX129801 doses of 1.33, 4 and 13.3 mg/kg, respectively (Table 2). Corresponding mean AUC values were 1180, 4210 and 13200 nM•day in males and 1280, 3920 and 11200 nM•day (Table 2).

CBX129801 exposure in female rats was higher than males, but displayed no apparent gender-related differences in monkeys (Tables 1 and 2 and Figures 1, 2, 4, 5 and 6).

CBX129801 apparent $T_{1/2}$ values ranged from 1.26 to 1.62 days in rats and the mean apparent $T_{1/2}$ values ranged from 2.63 to 4.67 days in monkeys (Tables 1 and 2).

The exposure following repeated doses was approximately equal to that following the first dose in rats and was slightly higher than that following the first dose in monkeys. The T_{max} and $T_{1/2}$ values did not change due to the increase in CBX129801 dose or repeated weekly dosing in both rats and monkeys (Tables 1 and 2).

CBX129801 concentrations in rats and monkeys appeared to achieve a steady state on Days 14 to 21. There were no statistical significant differences ($p > 0.05$) among CBX129801 concentrations on Days 14, 21 and 28 in both sexes (Figure 3 and 6).

CBX129801 TK parameters for the pooled gender in monkeys (combined male and female/dose) were comparable to the TK parameters for individual gender (see Table 2).

Table 1

* Expressed as median

Summary of CBX129801 Toxicokinetic Parameters in Rats Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study

Sex	Male			Female		
Dose, mg/kg/week	2.74	8.22	27.4	2.74	8.22	27.4
First Dose (TK)						
C_{max}, nM	156	440	1,540	412	564	2,210
T_{max}, day*	1.00	1.00	2.00	3.00	1.00	1.00
$T_{1/2}$, day	1.52	1.49	1.62	1.47	1.26	1.46
AUC_{inf}, nM•day	507	1,580	4,580	1,020	2,110	7,590
AUC_{inf}, nM•day	539	1,690	4,950	1,060	2,190	8,050
CL/F, mL/day/kg	108	104	118	55.1	79.9	72.5
V_z/F, mL/kg	237	223	275	117	146	153
C_{max} Male/Female Ratio	0.379	0.780	0.697	-	-	-
AUC_{inf} Male/Female Ratio	0.508	0.772	0.615	-	-	-
CL/F Male/Female Ratio	1.96	1.30	1.63	-	-	-
V_z/F Male/Female Ratio	2.03	1.53	1.80	-	-	-
Repeated Dose (TK)						
C_{max}, nM	156	440	1,540	412	564	2,210
T_{max}, day	1.00	1.00	2.00	3.00	1.00	1.00
$T_{1/2}$, day	1.52	1.49	1.62	1.47	1.26	1.46
AUC_{inf}, nM•day	507	1,580	4,580	1,020	2,110	7,590
CLss/F, mL/day/kg	539	1,690	4,950	1,060	2,190	8,050
V_{ss}/F, mL/kg	237	223	275	117	146	153
C_{max} Male/Female Ratio	0.473	0.518	0.402	-	-	-
AUC_{inf} Male/Female Ratio	0.481	0.570	0.433	-	-	-
CLss/F Male/Female Ratio	2.07	1.75	2.32	-	-	-
V_{ss}/F Male/Female Ratio	1.80	1.96	2.09	-	-	-
Repeated/First Dose C_{max} Ratio	0.942	0.995	0.695	0.755	1.50	1.20
Repeated/First Dose AUC_{inf} Ratio	1.03	1.08	0.906	1.07	1.42	1.26

Table 2

* Expressed as median

Summary of Mean CBX129801 Toxicokinetic Parameters in Monkeys Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study

Sex	Male			Female			Pooled Gender		
Dose, mg/kg/week	1.33	4	13.3	1.33	4	13.3	1.33	4	13.3
First Dose (TK)									
Cmax, nM	156	440	1,540	412	564	2,210	412	564	2,210
T_{max}, day*	1.00	1.00	2.00	3.00	1.00	1.00	3.00	1.00	1.00
T1/2, day	1.52	1.49	1.62	1.47	1.26	1.46	1.47	1.26	1.46
AUCtau, nM•day	507	1,580	4,580	1,020	2,110	7,590	1,020	2,110	7,590
AUCinf, nM•day	539	1,690	4,950	1,060	2,190	8,050	1,060	2,190	8,050
CL/F, mL/day/kg	108	104	118	55.1	79.9	72.5	55.1	79.9	72.5
Vd/F, mL/kg	237	223	275	117	146	153	117	146	153
Cmax Male/Female Ratio	0.379	0.780	0.697	-	-	-	-	-	-
AUCinf Male/Female Ratio	0.508	0.772	0.615	-	-	-	-	-	-
Repeated Dose (TK)									
Cmax, nM	308	1,250	3,780	371	1,350	4,900	340	1,300	4,340
T_{max}, day*	2.00	1.00	2.00	2.00	1.00	2.00	2.00	1.00	2.00
T1/2, day	4.78	2.93	3.91	4.62	3.34	3.07	4.70	3.17	3.49
AUCtau, nM•day	1,650	5,610	18,600	1,860	6,000	21,400	1,750	5,810	20,000
AUCtau, nM•day	2,740	7,330	28,300	2,910	8,240	28,300	2,820	7,790	28,300
CLss/F, mL/day/kg	18.3	15.7	15.8	15.9	14.7	13.6	17.1	15.2	14.7
Vdss/F, mL/kg	121	67.8	86.0	110	71.4	61.0	116	69.6	73.5
Cmax Male/Female Ratio	0.830	0.830	0.771	-	-	-	-	-	-
AUCtau Male/Female Ratio	0.887	0.935	0.869	-	-	-	-	-	-
Repeated/First Dose Cmax Ratio	1.23	1.42	1.36	1.47	1.54	2.04	1.35	1.48	1.68
Repeated/First Dose AUCtau Ratio	1.40	1.33	1.41	1.45	1.53	1.91	1.42	1.42	1.64

Figure 2

Mean Plasma Concentrations (nM) of CBX129801 in Rats Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study

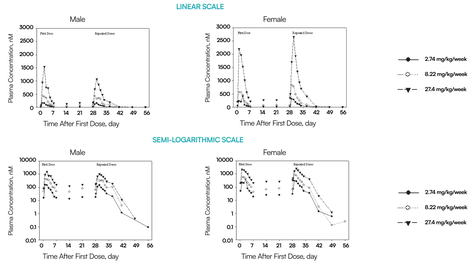


Figure 4

Mean Plasma Concentrations (nM) of CBX129801 in Monkeys Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study

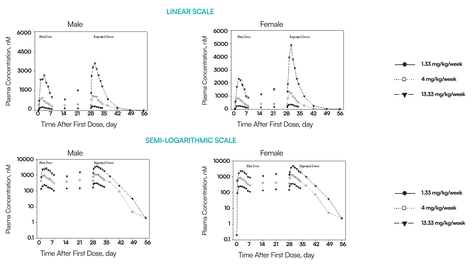


Figure 2

CBX129801 C_{max} and AUC_{inf} versus CBX129801 Dose in Rats Following CBX129801 in a 28-Day Toxicity Study

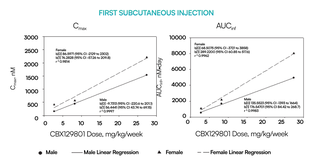
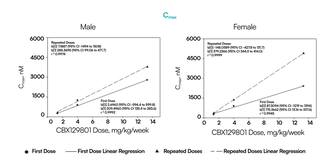
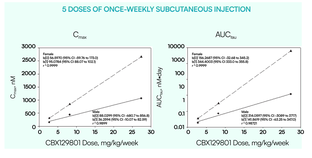


Figure 4

Mean CBX129801 C_{max} and AUC_{tau} versus CBX129801 Dose in Monkeys Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study





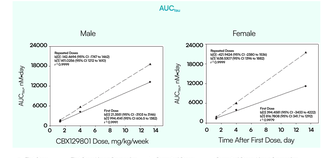


Figure 3

CBX129801 Dose-Normalized Predose Plasma Concentrations (nM/mg) in Rats Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study

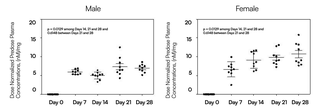
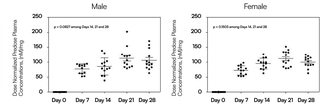


Figure 6

CBX129801 Dose-Normalized Predose Plasma Concentrations (nM/mg) in Monkeys Following Subcutaneous Injections of CBX129801 in a 28-Day Toxicity Study



Conclusions

CBX129801 was readily measurable in rat and monkey plasma with T_{max} ranging from 1 to 3 days. After subcutaneous administration, its exposure was dose proportional and was slightly higher in females (rats).

Repeated weekly dosing of CBX129801 resulted in no accumulation in rats and slight accumulation in monkeys. CBX129801 concentrations appeared to achieve a steady state on Days 14 to 21.

The PEGylation of C-peptide results in an extended half-life and sustained exposures of this bio-active peptide, which support a once-weekly clinical dosing regimen for CBX129801 as a potential replacement therapy in the treatment of the long-term complications of type 1 diabetes such as peripheral neuropathy.

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