W4402

Embryo-Fetal Developmental Toxicokinetic Study of CBX129801, a Bio-active C-peptide for Potential Replacement Therapy in Type 1 Diabetic Nephropathy, in Rats and Rabbits After Subcutaneous Injections

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ABSTRACT

Purpose: To evaluate the maternal toxicokinetics and fetal exposures of CBX129801 in studies which assessed the developmental toxicity, after subcutaneous injection for 4 doses to pregnant female rats and rabbits.

Methods: CBX129801 was administered to five groups of pregnant rats and rabbits by subcutaneous injection at 0, 3, 10, 30 or 100 mg/kg/dose for a total of 4 doses from Gestation Day (GD) 6 to GD 17 in rats and from GD 7 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_{max} values in rats ranged from 0.250 to 2.00 days and in rabbits from 1.00 to 2.00 days. C_{max} values in rats were 261, 907, 2640 and 9960 ng/mL and in rabbits were 359, 1240, 3880 and 13000 ng/mL for CBX129801 first dose of 3, 10, 30 or 100 mg/kg, respectively. Corresponding $AUC_{(0-T)}$ values were 549, 1880, 5950 and 21200 ng·day/mL in rats and 1050, 3780, 11500 and 37300 ng·day/mL in rabbits, respectively. $T_{1/2}$ values ranged from 0.837 to 1.00 day in rats and from 2.14 to 2.39 days in rabbits. T_{max} and $T_{1/2}$ did not change due to repeated dosing in both species. CBX129801 C_{max} and $AUC_{(0-T)}$ displayed dose proportional increases in both species. Repeated dosing resulted in no accumulation in rats and in 1.36- to 1.66-x accumulation in rabbits. The dam/fetal plasma concentration ratios ranged from 101- to 1360-x in rats and from 33.0- to 187-x in rabbits.

Conclusions: The exposure of CBX129801, as measured by C_{max} and $AUC_{(0-T)}$, increased in a dose proportional manner after single or repeated dosing. Half-life ranged from 0.837 to 1.00 day in rats and from 2.14 to 2.39 days in rabbits and were unaffected by repeated dosing. Repeated dosing resulted in no accumulation in rats and in 1.36- to 1.66-x accumulation in rabbits. The fetal exposure was minimal in both species.

Purpose

To evaluate the maternal toxicokinetics (TK) and fetal exposures of CBX129801 in studies which assessed the developmental toxicity, after subcutaneous injection of 4 doses to pregnant female rats and rabbits during the major period of organogenesis.

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. each year.

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

A protective effect of C-peptide treatment was demonstrated in preclinical and early clinical studies.

Cebix is developing a PEGylated C-peptide drug (CBX129801) for the treatment of long-term complications of diabetes. The PEG attaches to the single amino acid at the N-terminus leaving the biologically active C-terminus available. CBX129801 has an extended half-life as compared to unmodified native C-peptide (days as compared to minutes).

This work presents the maternal TK and fetal exposures of CBX129801 in pregnant female rats and rabbits.

Methods

Study Design

Five groups of pregnant rats and rabbits received a total of 4 subcutaneous doses of CBX129801 every 3-5 days from Gestation Day (GD) 6 to GD 17 in rats and from GD 7 to GD 21 in rabbits at 0, 3, 10, 30 or 100 mg/kg/dose. Maternal and fetal blood samples were collected at predetermined times.

Analytical Method

The plasma samples were analyzed for CBX129801 by validated ELISA assays.

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 CBX129801 Plasma Concentration-Time Profiles in Pregnant Rats Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/Fetal Developmental Study (GD 6, GD 9, GD 13 and GD 17)

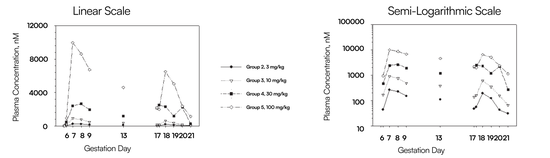

Figure 2

CBX129801 C_{max} and $AUC_{(0-3)}$ in Pregnant Rats as a Function of CBX129801 Dose in an Embryo/Fetal Developmental Study

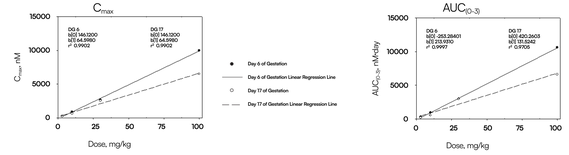

Figure 3

Mean CBX129801 Plasma Concentration-Time Profiles in Pregnant Rabbits Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/Fetal Developmental Study

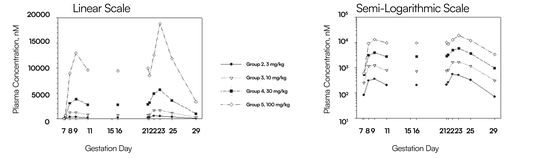

Figure 4

Mean CBX129801 C_{max} and $AUC_{(0-4)}$ in Pregnant Rabbits as a Function of CBX129801 Dose in an Embryo/Fetal Developmental Study

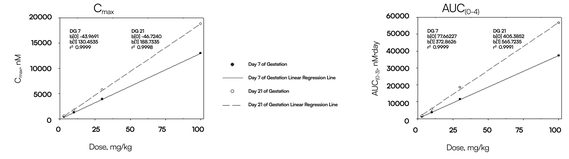

Table 1

Summary of TK Parameters of CBX129801 in Pregnant Rats Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/Fetal Developmental Study (GD 6, GD 9, GD 13 and GD 17)

TK Parameter	Dose, mg/kg			
	3	10	30	100
Gestation Day 6, 1st Dose				
C_{max}, ng/mL	261	907	2,640	9,960
T_{max}, day	1.00	1.00	2.00	1.00
$T_{1/2}$, day	ND	ND	ND	ND
$AUC_{(0-t)}$, nM·day	549	1,880	5,950	21,200
$AUC_{(0-\infty)}$, nM·day	ND	ND	ND	ND
CL/F, mL/day/kg	ND	ND	ND	ND
C_{max} Sex Ratio (M/F)	ND	ND	ND	ND
V_z/F, mL/kg	ND	ND	ND	ND
Gestation Day 17, 4th Dose				
C_{max}, ng/mL	195	617	2,510	6,500
T_{max}, day	1.00	1.00	0.250	1.00
$T_{1/2}$, day	1.00	0.837	ND	0.931
$AUC_{(0-t)}$, nM·day	349	1,060	5,880	13,200
$AUC_{(0-\infty)}$, nM·day	386	1,170	7,140	14,900
CL/F, mL/day/kg	166	182	89.6	143
V_z/F, mL/kg	240	220	ND	192
4th Dose/1st Dose C_{max} Ratio	0.747	0.680	0.951	0.653
4th Dose/1st Dose $AUC_{(0-t)}$ Ratio	0.636	0.564	0.988	0.623
GD 21 Dam Plasma Concentration, nM	30.8	65.9	274	1,140
GD 21 Fetal/Pup Plasma Concentration, nM	0.306	0.00	0.00	1.54
Dam/Offspring Plasma Ratio[a]	101	ND	ND	740

[a] Value represents the ratio of Day 21 dam concentration to the average corresponding fetal/pup concentrations (i.e., 1,140/0.839).

ND - Not Determined

Table 2

Summary of Mean TK Parameters of CBX129801 in Pregnant Rabbits Following Repeated Subcutaneous Injection of CBX129801 in an Embryo/Fetal Developmental Study (GD 7, GD 11, GD16 and GD 21)

TK Parameter[a]	Dose, mg/kg			
	3	10	30	100
Gestation Day 7, 1st Dose				
C_{max}, ng/mL	359	1,240	3,880	13,000
T_{max}, d[b]	2.00	2.00	2.00	2.00
$T_{1/2}$, d[c]	ND	ND	ND	ND
$AUC_{(0-t)}$, nM·day	1,050	3,780	11,500	37,300
$AUC_{(0-\infty)}$, nM·day	ND	ND	ND	ND
CL/F, mL/day/kg	ND	ND	ND	ND
C_{max} Sex Ratio (M/F)	ND	ND	ND	ND
V_z/F, mL/kg	ND	ND	ND	ND
Gestation Day 21, 4th Dose				
C_{max}, ng/mL	562	1,690	5,750	18,800
T_{max}, d[b]	1.00	1.00	2.00	2.00
$T_{1/2}$, d[c]	2.14	2.39	ND	ND
$AUC_{(0-t)}$, nM·day	1,740	5,580	18,500	56,700
$AUC_{(0-\infty)}$, nM·day	2,040	6,610	21,800	61,500
$AUC_{(0-192)}$, nM·day	2,540	8,480	27,600	87,200
CL/F, mL/day/kg	31.7	33.4	29.4	31.7
V_z/F, mL/kg	92.6	107	ND	ND
4th Dose/1st Dose C_{max} Ratio	1.57	1.36	1.48	1.45
4th Dose/1st Dose $AUC_{(0-t)}$ Ratio	1.66	1.48	1.61	1.52
Dam Plasma Concentration, nM[d]	70.9	311	959	3,390
Fetal Plasma Concentration, nM[d]	1.42	1.66	2.91	68.8
Dam/Fetal Plasma Ratio	49.9	187	330	48.7

[a] Mean CBX129801 TK parameters based on three rabbits per dose group
[b] Expressed as median
[c] Expressed as harmonic mean
[d] 192 hours post-dose
ND - Not Determined

Results

CBX129801 was readily measurable in plasma of both species with T_{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 3).

In rats, CBX129801 C_{max} values following the first dose were 261, 907, 2640 and 9960 ng/mL and $AUC_{(0-T)}$ values were 549, 1880, 5950 and 21200 ng·day/mL for CBX129801 doses of 3, 10, 30 or 100 mg/kg, respectively (Table 1).

In rabbits, mean CBX129801 C_{max} values following the first dose were 359, 1240, 3880 and 13000 ng/mL and mean $AUC_{(0-T)}$ values were 1050, 3780, 11500 and 37300 ng·day/mL for CBX129801 doses of 3, 10, 30 or 100 mg/kg, respectively (Table 2).

CBX129801 TK exposure (C_{max} and $AUC_{(0-T)}$) was dose proportional in both species (Tables 1 and 2 and Figures 2 and 4).

CBX129801 apparent $T_{1/2}$ values ranged from 0.837 to 1.00 day in rats and the mean apparent $T_{1/2}$ values ranged from 2.14 to 2.39 days in rabbits (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 (1.36- to 1.66-x) that following the first dose in rabbits (Tables 1 and 2).

The T_{max}, $T_{1/2}$, Vd/F and CL/F values did not change due to the increase in CBX129801 dose or repeated dosing in both species (Tables 1 and 2 and Figures 1 and 2).

The dam/fetal plasma concentration ratios ranged from 101- to 1360-x in rats and from 33.0- to 187-x in rabbits (Tables 1 and 2).

Conclusions

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

Half-life ranged from 0.837 to 1.00 day in rats and from 2.14 to 2.39 days in rabbits and were unaffected by repeated dosing. 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; however, some limited fetal exposure was present.

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References

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

Acknowledgements

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