M1117

Pharmacokinetics of Subcutaneously-administered CBX129801, A Long-acting Synthetic C-Peptide in Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Purpose:

To assess the pharmacokinetics (PK) of CBX129801, a long-acting synthetic C-peptide, following subcutaneous (SC) injection in patients with type 1 diabetes mellitus (T1DM).

Methods:

This was a phase 1 randomized, double-blind, placebo-controlled, single and multiple ascending dose study to assess the safety, tolerability, and PK of CBX129801 administered SC in patients with T1DM. Single doses of 0.3, 1.0, and 3.3 mg were evaluated in 3 sequential cohorts (A, B and C, respectively). Subjects were randomized to CBX129801 (n=8) or placebo (n=2) per cohort. Three weeks later, 4 additional doses (in Cohorts A and B) or 3 additional doses (in Cohort C) were administered at weekly intervals. Plasma CBX129801 concentrations were quantified by an ELISA and PK parameters were determined by noncompartmental analysis. Dose proportionality was assessed for single and multiple dose separately using the power-law model.

Results:

After single doses, median plasma CBX129801 T_{max} ranged from 3.11 to 4.93 days. The mean C_{max} values were 0.269, 0.975 and 4.13 nM for the 0.3, 1 and 3.3 mg doses, respectively. Corresponding mean AUC_∞ values for the two higher doses were 14.5 and 60.4 nM-d. $t_{1/2}$ were 6.37 and 6.92 days, CL/F were 1.59 and 1.38 L/d and V_z/F were 14.3 and 12.7 L, respectively.

The $t_{1/2}$, AUC_∞, CL/F and V_z/F were incalculable at the 0.3 mg dose since it was not possible to estimate λ_z. Dose proportionality assessment showed the slope (90% Confidence Interval; CI) for dose and Log_{10} C_{max} was 1.116 (0.9631 to 1.268) and for Log_{10} AUC_∞ was 1.154 (0.8709 to 1.437).

After repeated doses, mean T_{max} ranged from 1.98 days to 2.99 days, mean C_{max} values were 0.718, 2.30, and 11.2 nM, mean C_{min} values were 0.469, 1.73, and 6.82 nM and mean AUC_τ values were 4.31, 14.2, and 66.7 nM-d at the 0.3, 1.0, and 3.3 mg/week repeated doses, respectively. CBX129801 exposure following repeated doses was slightly more than dose proportional; the slope (90% CI) for dose and Log_{10} C_{max} was 1.150 (1.051 to 1.248) and for Log_{10} AUC_τ was 1.148 (1.054 to 1.243). The T_{max} and $t_{1/2}$ were similar following single and repeat dosing.

Conclusions:

CBX129801 exposure in patients with T1DM was approximately dose proportional, single dosing was predictive for multiple dosing, and the half-life supports weekly dosing.

Purpose

To assess the single and multiple dose pharmacokinetics (PK) of CBX129801 following subcutaneous (SC) injection in patients with type 1 diabetes mellitus (T1DM).

Introduction

Type 1 diabetes mellitus (T1DM) affects about 1.4 million people in the US and 10 to 20 million worldwide (1, 2). In the US, 30,000 new cases are diagnosed annually and 40% of those diagnosed are under the age of 20 years (3, 4). Type 1 diabetes is characterized by the body's inability to produce proinsulin and consequently both insulin and C-peptide. The plasma C-peptide concentration in patients with T1DM is below 0.1 nM relative to the physiological range in healthy subjects of 0.4-6 nM (5, 6). Diabetic neuropathy (DPN) affects about half of all people with diabetes at some point in their lifetimes.

Preclinical and early clinical studies demonstrated that the administration of C-peptide showed protective effect against the long-term complications of T1DM, including DPN. However, the short half-life of C-peptide aqueous formulation (~65 min) precludes its clinical applicability (7). Cebix Inc. is developing CBX129801, a long-acting PEGylated synthetic C-peptide that supports weekly SC dosing, to treat the long-term complications of diabetes. This poster presents the PK of CBX129801 in patients with T1DM (Clinical Trial Registration Number: NCT01293461).

METHODS

Study:

A phase 1 randomized, double-blind, placebo-controlled, single and multiple ascending dose study to assess the safety, tolerability, and PK of CBX129801 administered SC in patients with T1DM.

Dose

Part 1:
Escalating doses of 0.3, 1.0, and 3.3 mg were administered in 3 sequential cohorts (A, B and C, respectively). Within each cohort, subjects were randomized to CBX129801 (n=8) or placebo (n=2) and a single dose was administered. Three weeks later, 4 additional doses (in Cohorts A and B) or 3 additional doses (in Cohort C) were administered at weekly intervals. Blood samples were collected at the end of the predetermined times over 672 hours. Pre-dose (trough) samples were collected for all doses and at the end of the dosing interval after the last dose.

Part 2:
After review of the PK data from Part 1 of the study, in order to select a dose regimen to achieve a target C-peptide "replacement" plasma concentration at steady-state, subjects in Part 2 (Cohort D) were randomized to CBX129801 (n=29) or placebo (n=13). A loading dose of 2.0 mg was administered and 1 week later, 12 maintenance doses of 0.8 mg were administered at weekly intervals. Blood samples were collected pre-dose (trough) for the first and second doses, then before every other dose from the third through the eleventh doses and at the end of the dosing interval after the last dose.

Analytical Method

Plasma CBX129801 concentrations were quantified by an ELISA assay.

PK Analysis

- PK analyses were performed using noncompartmental method (8) with validated WinNonlin Professional 6.1.1 (Pharsight Corp., Mountain View, CA, USA).
- Dose proportionality was examined using a power-law model (p value set at $p \geq 0.05$) (9, 10) with GraphPad Prism v 5.01 (GraphPad Inc., CA, USA).

$$\log C_{max} \text{ or } \log AUC = \log(\boldsymbol{\mu}) + \beta \times \log dose + \boldsymbol{\varepsilon}$$

where $\log(\mu)$ and β, and ε are the intercept, slope and the random error, respectively. A slope of 1.00 indicates perfect dose proportionality, a slope of less than 1.00 or greater than 1.00 indicates less than or greater than dose proportional, respectively (90% CI for the slope should include 1.00).

Table 1

Summary of Plasma CBX129801 PK Parameters Following the First Dose in Part 1

Dose, mg	0.3			1.0			3.3		
PK Parameter	n	Mean	%CV	n	Mean	%CV	n	Mean	%CV
C_{max}, nM	3	0.269	7.24	8	0.975	23.4	8	4.13	43.3
T_{max}, d*	3	3.11	(2.98-8.86)	8	4.91	(2.85-6.94)	8	4.93	(2.98-5.02)
AUC_{0-t}, nM-d	3	1.38	13.9	8	11.8	32.1	8	49.7	45.4
$AUC_{0-\infty}$, nM-d	1	1.42	NC	8	5.28	28.6	8	22.4	45.6
$AUC_{0-\tau}$, nM-d	0	NC	NC	8	14.5	29.6	8	60.4	45.0
%AUCextrap	0	NC	NC	8	19.0	26.7	8	16.2	55.6
$t_{1/2}$, d	0	NC	NC	8	6.37	16.4	8	6.92	40.9
CL/F, L/d	0	NC	NC	8	1.59	33.3	8	1.38	42.0
V_z/F, L	0	NC	NC	8	14.3	26.9	8	12.7	45.0
t_{lag}, d*	3	0.997	(0.238-0.997)	8	0.239	(0.0833-0.253)	8	0.0844	(0-0.25)

NC - Not calculated
* Expressed as median and range
sd - Single Dose

Table 1

Summary of Plasma CBX129801 PK Parameters Following the Last Dose (Fourth or the Fifth Dose) in Part 1

Dose, mg	0.3			1.0			3.3		
PK Parameter	n	Mean	%CV	n	Mean	%CV	n	Mean	%CV
C_{max}, nM	7	0.718	29.2	8	2.30	11.0	8	11.2	29.5
C_{min}, nM	7	0.469	26.6	8	1.73	11.8	8	6.82	32.1
C_{av}, nM	7	0.615	28.1	8	2.04	13.4	8	9.02	27.5
T_{max}, d*	7	2.99	(0.972-7.00)	8	1.98	(0-3.03)	8	2.45	(1.90-4.94)
AUC_{0-t}, nM-d	7	8.14	37.1	8	26.9	21.8	8	154	36.1
$AUC_{0-\tau}$, nM-d	7	4.31	28.1	8	14.2	13.4	8	66.7	27.5
$t_{1/2}$, d	6	7.92	41.2	8	6.35	16.0	8	6.33	27.8
CL_{ss}/F, L/d	7	1.62	34.1	8	1.52	12.7	8	1.13	26.4
V_{ss}/F, L	6	21.8	84.1	8	13.7	12.5	8	10.4	44.8
AUC_{0-t} / $AUC_{0-\tau}$	0	NC	NC	8	1.04	23.6	8	1.22	34.6
RC_{max}	2	3.29	12.5	8	2.44	19.4	8	3.01	39.2
$RAUC_\tau$	1	3.70	NC	8	2.90	30.2	8	3.41	45.2

NC - Not calculated
R_{AUC}, accumulation index for AUC calculated from AUC_τ
R_{max}, accumulation index for C_{max} calculated from C_{max}
* Expressed as median and range

sd - Single Dose
md - Multiple Dose

Figure 1

Mean (± SD) Plasma CBX129801 Concentration-Time Profiles in Part 1

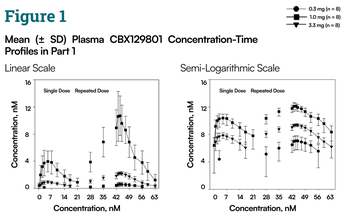
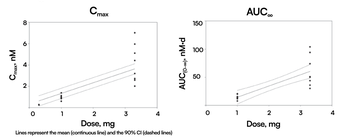


Figure 2

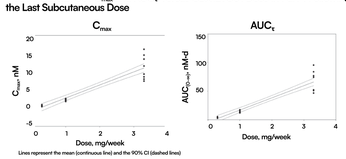
Plasma CBX129801 C_{max} and AUC_∞ Versus CBX129801 Dose in Part 1 Following the First Subcutaneous Dose



Lines represent the mean (continuous line) and the 90% CI (dashed lines)

Figure 3

Plasma CBX129801 C_{max} and AUC_τ Versus CBX129801 Dose in Part 1 Following the Last Subcutaneous Dose



Lines represent the mean (continuous line) and the 90% CI (dashed lines)

Table 3

Statistics for the Assessment of Dose Proportionality of Plasma CBX129801 Exposure in Part 1

Parameter	n	Slope Mean (SE)	90% CI	p-value (Slope=1)
Single Dose				
$Log\ C_{max}$	19	1.116 (0.08775)	0.9631 to 1.268	0.2045
$Log\ AUC_\infty$	16	1.154 (0.1607)	0.8709 to 1.437	0.3544
Multiple Dose				
$Log\ C_{max}$	19	1.150 (0.06749)	1.051 to 1.248	0.0167
$Log\ AUC_\tau$	23	1.148 (0.05481)	1.054 to 1.243	0.0133

Table 4

Summary of Predose Plasma CBX129801 Concentrations (nM) in Part 2

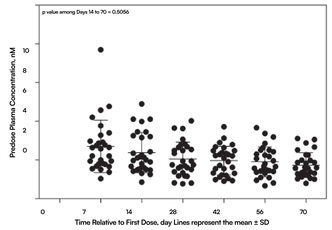
Parameter	n	Mean (SE)	p-value (Slope=1)
0	28	0.00	NC
7	29	2.70	50.0
14	29	2.38	43.6
28	29	2.04	43.1
42	29	1.97	37.6
56	29	1.90	40.5
70	29	1.73	37.1
84	29	1.82	32.3
EOS	29	NC	NC

EOS - End of Study
NC - Not Calculated
Each subject received a single 2.0 mg SC loading dose followed by 11 weekly 0.8 mg SC doses starting on Day 8 (i.e., a total of 12 doses administered). The last dose was on Day 78.

Figure 4

Mean Predose Plasma CBX129801 Concentrations in Part 2

Semi-Logarithmic Scale



Each subject received a single 2.0 mg SC loading dose followed one week later by 11 weekly 0.8 mg SC doses starting on Day 8 (i.e., a total of 12 doses administered).

Results

SINGLE AND MULTIPLE DOSE PK OF CBX129801

Single Ascending Dose

- Median T_{max} ranged from 3.11 to 4.93 days and the median t_{lag} ranged from 0.0844 to 0.997 days (i.e., 2 to 24 hours) (Table 1).
- Mean C_{max} values were 0.269, 0.975 and 4.13 nM for the 0.3, 1 and 3.3 mg doses, respectively. Mean AUC_∞ values were 14.5 and 60.4 nM-d. $t_{1/2}$ values were 6.37 and 6.92 days, CL/F values were 1.59 and 1.38 L/d and V_z/F values were 14.3 and 12.7 L for the 1.0 and 3.3 mg doses, respectively (Table 1).
- It was not possible to estimate λ_z for the 0.3 mg dose, so $t_{1/2}$, AUC_∞, CL/F and V_z/F were incalculable.
- After single doses, CBX129801 exposure was dose proportional with slope for Cmax of 1.116 and for AUC∞ was 1.154. The corresponding 90% CI were 0.9631 to 1.268 and 0.8709 to 1.437, respectively (Table 3 and Figure 2).

Multiple Ascending Dose

- Median T_{max} ranged from 1.98 days to 2.99 days and the mean $t_{1/2}$ values ranged from 6.33 to 7.92 days (Table 2). Tmax and $t_{1/2}$ were not dose dependent and were similar following single and repeat dosing (Tables 1 and 2).
- Mean C_{max} values were 0.718, 2.30, and 11.2 nM, mean C_{min} values were 0.469, 1.73, and 6.82 nM and mean AUC_τ values were 4.31, 14.2, and 66.7 nM-d for CBX129801 doses of 0.3, 1.0, and 3.3 mg/week, respectively. The mean CL_{ss}/F values were 1.62, 1.52 and 1.13 L/d and mean V_{ss}/F values were 21.8, 13.7 and 10.4 L for the 0.3, 1.0, and 3.3 mg/week doses, respectively (Table 2).
- CL_{ss}/F and V_{ss}/F appeared to decrease as the dose of CBX129801 increased (Table 2).
- After repeated doses, CBX129801 exposure was slightly greater than dose proportional with slope for C_{max} of 1.150 and for AUC_τ of 1.148. The corresponding 90% CI were 1.051 to 1.248 and 1.054 to 1.243, respectively (Table 3 and Figure 3).

ASSESSMENT OF REPEATED DOSING

- Following repeated doses, CBX129801 exhibited moderate accumulation (Table 2 and Figure 1). The mean RCmax (accumulation index for Cmax) values were 3.29, 2.44 and 3.01 for the 0.3, 1.0 and 3.3 mg/week doses, respectively. Corresponding mean RAUC (accumulation index for AUC) values were 3.70, 2.90 and 3.41 (Table 2).
- The T_{max}, $t_{1/2}$ CL_{ss}/F and V_{ss}/F did not change due to repeated dosing of CBX129801 (Tables 1 and 2).

ATTAINMENT OF STEADY-STATE

- CBX129801 predose concentrations on Days 0, 7, 14, 28, 42, 56 and 70 in Part 2 suggested that steady state was likely achieved by Day 28 as presented in Table 4 and displayed in Figure 4.
- Steady-state mean predose plasma CBX129801 concentrations between Day 28 and Day 84 ranged from 1.73 to 2.04 nM (Table 4).

Conclusions

- All the doses assessed in the study were safe and well tolerated.
- CBX129801 exposure was dose proportional following the single doses and slightly greater than dose proportional following the repeated doses.
- The T_{max} and $t_{1/2}$ were not dose dependent following single or repeated doses.
- The CL/F and V_z/F were not dose dependent following the single doses and appeared to decrease as the dose increases following the repeated doses.
- The mean $t_{1/2}$ ranged from 6.33 to 7.92 days which is 150x greater than the native C-peptide $t_{1/2}$ and supports weekly SC dosing of CBX129801.
- Moderate accumulation of CBX129801 was observed and is consistent with the long $t_{1/2}$.
- Steady state was achieved by Day 28.
- Using SC doses of 0.3 mg - 3.3 mg CBX129801 administered at weekly intervals, it is possible to achieve plasma CBX129801 concentrations in patients with T1DM that are broadly within the physiological range of C-peptide concentrations observed in non-diabetic individuals (0.4 nM - 6 nM).

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