A phase Ib study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of the hepcidin antagonist PRS-080#022-DP in anemic chronic kidney disease patients undergoing hemodialysis

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Anticalin bound to the peptide Hepcidin

Introduction

The hepatic hormone hepcidin was identified as an important regulator of iron metabolism in chronic diseases and offers a new target to treat anemia of chronic disease (Figure 1). Elevated levels of hepcidin contribute to functional iron deficiency and anemia by restricting iron to the reticulo-endothelial system and thereby reducing its availability for erythropoiesis. Thus, antagonizing hepcidin has the potential to improve iron availability and erythropoiesis, while avoiding overload with exogenous iron and reducing the administered levels of ESAs (1). PRS-080#022-DP is an Anticalin® drug candidate derived from the naturally occurring human neutrophil gelatinase-associated lipocalin. The 20kD protein is linked to a 30kD linear poly-ethylene-glycol that specifically binds to human hepcidin 25, thereby inhibiting its activity.

Here we report first data on safety, pharmacokinetics (PK) and pharmacodynamic (PD) of single doses of PRS-080#022-DP in anemic patients with chronic kidney disease (CKD) requiring hemodialysis.

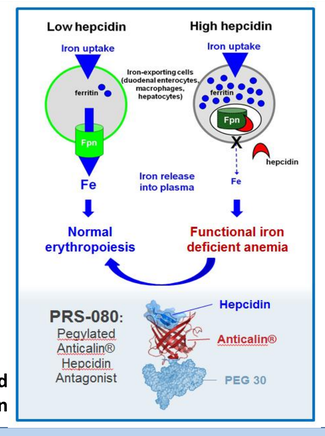

Figure 1: Iron metabolism regulated by hepcidin/ferroportin

Methods and Study design

In this multi-center, placebo-controlled, double-blind Phase Ib study, 24 anemic stage 5 CKD patients were treated with single ascending doses of PRS-080#022-DP in 3 cohorts at 2, 4, and 8 mg/kg body weight. Male (17) and post-menopausal female patients (7) of 55 ±14 years and 77 ±14 kg body weight, on hemodialysis for at least 90 days, on stable ESA dose, with Hb value of 9-12g/dL, ferritin ≥300 ng/mL, TSAT ≤40% and hepcidin of 5-75 nmol/L were included.

Iron treatment was not allowed from 7 days before until 7 days after study treatment. 6 patients per cohort received PRS-080#022-DP and 2 patients received placebo. Placebo or active treatments were administered by i.v. infusion over 1 h.

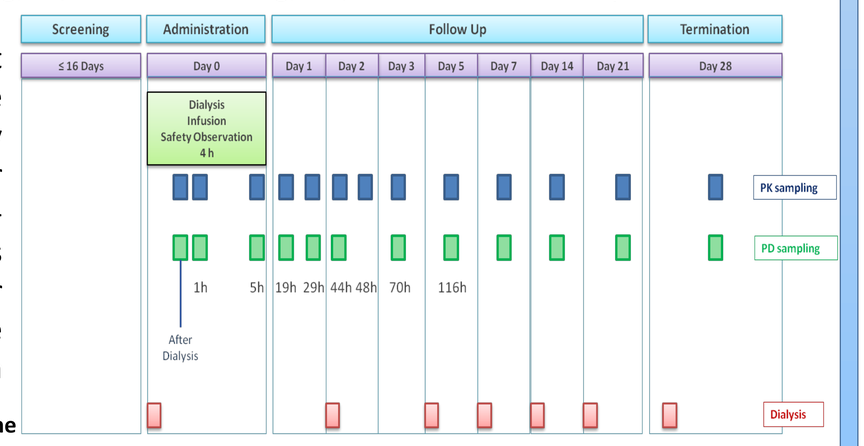

Figure 2: Study outline

Results

Safety

PRS-080#022-DP was safe and well tolerated. In total, 22 treatment-emergent adverse events (TEAEs) occurred in 12 patients (placebo and drug-treated patients).

One serious adverse event (dry gangrene) occurred after dosing with 2 mg/kg but was judged not related to PRS-080#022-DP. PRS-080#022-DP related adverse events (AEs) occurred in 2 patients and included "exercise tolerance decreased"

Table 1: Overview of adverse events reported during the study

	Treatment														
	PLACEBO			PRS-080#022-DP									TOTAL		
				2 mg/kg			4 mg/kg			8 mg/kg					
	N#	N	%	N#	N	%	N#	N	%	N#	N	%	N#	N	%
AEs	4	3	50.0	8	5	83.3	10	4	66.7	1	1	16.7	23	13	54.2
Pre-TEAEs	1	1	16.7	-	-	-	-	-	-	-	-	-	1	1	4.2
TEAEs[1]	3	2	33.3	8	5	83.3	10	4	66.7	1	1	16.7	22	12	50.0
TEAEs related to study drug	-	-	-	1	1	16.7	2	1	16.7	-	-	-	3	2	8.3

[1] One of these is a serious not drug related adverse event.
AEs = adverse events, N# = number of adverse events, N = number of patients with adverse event, % = Percent of patients with adverse event, TEAEs = treatment-emergent adverse events.

(1 patient in 2 mg/kg dose group) and "abdominal discomfort" and "headache" (1 patient 4 mg/kg dose group). The most frequently reported TEAEs were administration site conditions (edema and swelling) with 4 events, gastrointestinal disorders (abdominal discomfort, anal fissure, nausea, and vomiting) and vascular disorders (dry gangrene, hypertension and hypotension) with 4 events each. Most of the TEAEs were only reported once, except nausea (1 event in 4 and 8 mg/kg dose group) and cough (1 event in 2 and 4 mg/kg dose group). No dose-dependent increase of AEs was observed. Notably, vital signs, temperature and ECG were unchanged following administration.

Conclusion

The very good safety profile and the activity of PRS-080#022-DP on iron metabolism observed in anemic dialysis dependent end-stage CKD patients warrant further investigation of PRS-080#022-DP in a multiple dosing regimen to explore potential amelioration of anemia in stage 5 CKD patients.

Topic Nephrology

Reference
1 A Phase I Study Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Activity of the Hepcidin Antagonist PRS-080#022. Results from a Randomized, Placebo Controlled, Double-Blind Study Following Single Administration to Healthy Subjects; ASH 57 annual meeting & exposition, Dec. 5-8, 2015.

Financial disclosure statement
L. Matis and U. Moebius are co-worker of Pieris Pharmaceuticals, Inc., all other authors have financial relationships with Pieris Pharmaceuticals, Inc. and received payment for study participation.

Results

PK of FREE and TOTAL PRS-080#22-DP

Maximum concentration (C_{max}) and areas under the time curve (AUC) of FREE and TOTAL (free and bound to hepcidin) PRS-080#22-DP show a dose proportional increase.

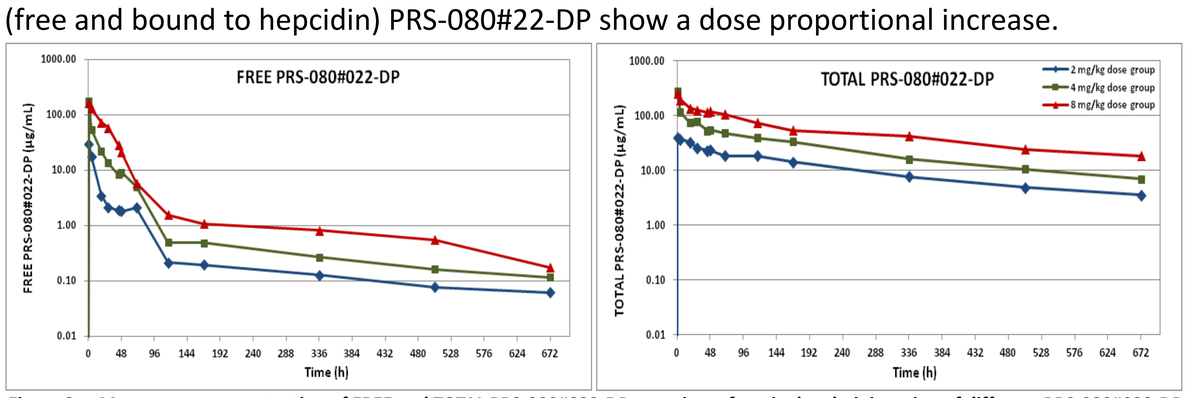

Figure 3: Mean serum concentration of FREE and TOTAL PRS-080#022-DP over time after single administration of different PRS-080#022-DP doses - semi-logarithmic scale

The plasma concentration profile of PRS-080#022-DP can be described by applying a two-exponential model with a fast first distribution phase and a much longer and slower second disposition phase. C_{max} of FREE and TOTAL PRS-080#022 were generally reached within 1 h after start of the infusion and declined dose-dependently with a first disposition phase and dose-independently in the final disposition phase (see half-life in Table 2).

Table 2: Mean pharmacokinetic parameters of FREE and TOTAL PRS-080#22-DP

		PRS-080#022-DP					
		2 mg/kg		4 mg/kg		8 mg/kg	
		FREE	TOTAL	FREE	TOTAL	FREE	TOTAL
N		6	6	6	6	6	6
C_{max}	[µg/mL]	30	45	174[#]	112	164	255
t_{max}	[h]	1	1	1	5	1	1
$AUC_{(0\text{-}672\ h)}$	[µg/mL*h]	504	7373	2038	17095	5020	37068
C_{max}/D	[µg/mL/mg]	14.86	22.33	43.53	27.88	20.50	31.88
$AUC_{(0\text{-}672\ h)}/D$	[µg/mL*h/mg]	251.97	3686.66	509.59	4273.81	627.46	4633.52
$t_{1/2\alpha}$	[h]	6.14	9.92	12.49	18.31	16.45	13.93
$t_{1/2\beta}$	[h]	284	200	247	196	231	263

[#] High variability of the data in the 4 mg/kg dose group.
AUC = area under the curve, C_{max} = maximum concentration, D = dose, $t_{1/2}$ = half-life time, t_{max} = time of maximum concentration.

Iron mobilization by PRS-080#22-DP

PRS-080#022-DP dose-dependently mobilized serum iron with increases in both serum iron concentration and TSAT following treatment (Figure 4). The serum C_{max} of iron and TSAT was reached 19h after infusion at all 3 doses.

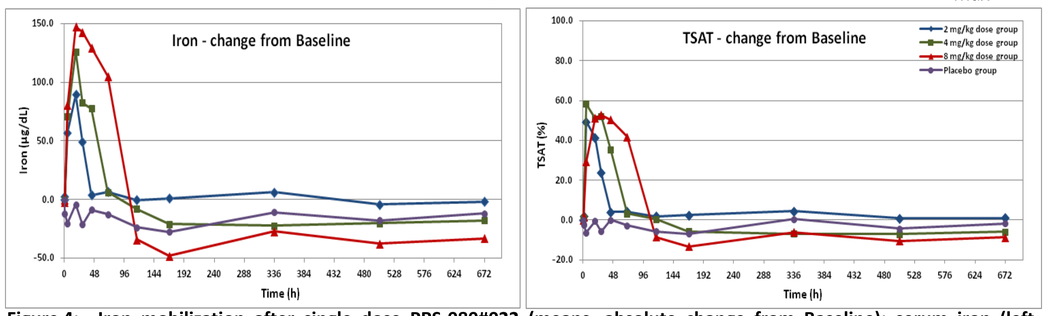

Figure 4: Iron mobilization after single dose PRS-080#022 (means, absolute change from Baseline): serum iron (left panel), and TSAT (right panel).

The duration of elevated serum iron concentration and TSAT increased dose-proportionally as well.

Table 3: Mean AUC values of serum iron profiles at different time intervals after i.v. administration of different doses of PRS-080#022-DP or PLACEBO

	Mean AUC [µg/dL*h] of time interval				
Dose group	0-672 h	0-44 h	0-70 h	0-116 h	0-168 h
2 mg/kg	2892.9	2397.6	2531.9	2669.9	2682.9
4 mg/kg	-6425.0	3757.7	**4847.5**	4805.3	4047.0
8 mg/kg	-9497.3	5790.6	8693.9	**10154.4**	7792.8
PLACEBO	-11299.1	-604.8	-884.3	-1723.8	-3067.1

AUC = area under the curve

After infusion of 2, 4, and 8 mg/kg PRS-080#022-DP, the mean serum iron concentration reached its baseline value after 2, 3 and between 4 and 5 days after the end of the infusion, respectively. AUCs of serum iron at different time points are shown Table 3.

Additionally, preliminary data of the study show that administration of PRS-080#022-DP resulted in a decrease of free hepcidin shortly after i.v. infusion (data not shown). Serum ferritin levels were largely unaffected by treatment at all three doses. No dose dependency was observed. These findings provide evidence that the serum iron mobilization is independent of the initial serum ferritin and initial TSAT values.