Safety, tolerability, and pharmacodynamics of the hepcidin antagonist PRS-080#022-DP after single administration - a phase Ib study in anemic chronic kidney disease patients undergoing hemodialysis

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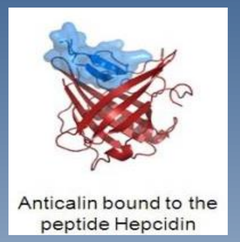

Anticalin bound to the peptide Hepcidin

Introduction Hepcidin plays a major role in the regulation of the iron metabolism in patients with functional iron deficiency (FID) anemia. Elevated levels of hepcidin restrict iron availability.

PRS-080#022 a 20kD Anticalin® protein linked to 30kD linear poly-ethylene-glycol, is developed for the treatment of FID anemia associated with chronic kidney disease. It specifically binds to human hepcidin 25, thereby inhibiting its activity. By antagonizing hepcidin PRS-080#022 has the potential to improve iron availability and erythropoiesis, while avoiding overload with exogenous iron and reducing the administered levels of ESAs [1]. First data of this randomized, placebo controlled phase I study have already been presented on the ERA-EDTA congress in Spain, 2017 [2]. Here we show further results of single doses of PRS-080#022-DP in anemic patients with chronic kidney disease (CKD) requiring hemodialysis.

Methods and Study Design

Study designs: Randomized, placebo-controlled, double-blind, multi-center study.
Main inclusion criteria: Chronic hemodialysis for ≥ 90 days, anemia of CKD, stable condition, blood hemoglobin 9.0 to 12.0 g/dL, transferrin saturation (TSAT) < 40%, ferritin > 300 ng/mL; plasma hepcidin (by mass spectrometry) 5.0 to 75 nmol/L.
Main exclusion criteria: Anemia of other cause; malignancy; infection with hepatitis B, C, or HIV; IV iron within 1 week prior to and after study medication.
Study protocol: Single IV injection of study medication; 4 weeks of follow-up; 3 cohorts with 8 patients per cohort, each cohort consisting of 6 study drug and 2 placebo treatments; increment doses of 2, 4, and 8 mg/kg from the first to the last cohort.

	Demographic data					Mean concentrations with standard deviation at screening		
	N	Mean Body weight [kg]	Mean Age [years]	Mean BMI [kg/m²] [calc.]	Gender	Hepcidin Plasma [nM]	TSAT [%]	Ferritin [ng/ml]
Treatment								
Placebo	6	73.32 ±10.73	54.0 ±13.2	26.50 ±4.13	3 males/ 3 females	31.3 ± 3.8	22.2 ±8.5	680.0 ±309.3
2 mg/kg	6	73.08 ±17.82	59.5 ±10.3	26.22 ±5.54	4 males /2 females	18.1 ±7.7	25.5 ±10.9	539.7 ±387.3
4 mg/kg	6	76.38 ±17.81	59.2 ±15.7	24.62 ±6.46	5 males /1 females	22.1 ±11.8	21.5 ±7.9	715.0 ±404.8
8 mg/kg	6	85.42 ±9.33	49.0 ±17.4	28.58 ±3.82	5 males /1 females	30.7±9.2	23.8 ±4.3	888.8 ±376.3
Total	**24**	**77.05 ±14.43**	**55.4 ±14.1**	**26.56 ±4.88**	**17 males/7females**	**25.6 ±11.7**	**23.3 ±7.9**	**705.9 ±368.7**

Table 1: Baseline patient characteristics

Pharmacodynamics

PRS-080#022-DP mobilizes serum iron with increases in both serum iron concentration and TSAT following treatment (Figures 1 and 2).

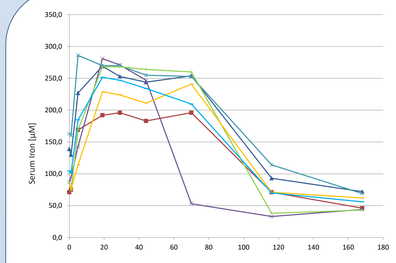

Figure 1: Mean and individual Iron concentrations of patients treated with 8 mg/kg bw

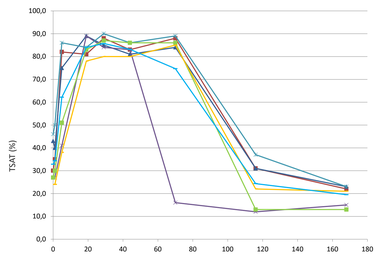

Figure 2: Mean and individual TSAT concentrations of patients treated with 8 mg/kg bw

We have previously shown that both iron and TSAT reach maximal levels 19 hours after infusion at all 3 dose levels studied (2, 4, and 8 mg/kg) [2]. We also showed that the magnitude and duration of elevated serum iron levels and TSAT concentrations increase dose-proportionally.

As shown in Figure 1, following treatment with PRS-080#022-DP 8 mg/kg, iron levels rise and then return to baseline values between 5 and 7 days after the end of the infusion, which is a longer duration of iron mobilization when compared to the 2 and 4 mg/kg doses [2]. As also shown in Figures 1 and 2 for patients receiving 8 mg/kg PRS-080#022-DP, the TSAT and iron levels show identical time profiles, indicating that most of the iron is transferrin bound.

Compared to Placebo, Ferritin levels are not affected by the single administration of PRS-080#022-DP in all three dose groups (Figure 3). In addition, initial plasma ferritin concentrations appear to have no influence on maximal concentration of iron after the different treatments.

Maximum serum iron mobilization appeared to correlate with baseline TSAT levels across all dose groups, such that patients with lower initial TSAT levels showed higher C_{max} iron increases following PRS-080#022-DP mediated hepcidin inhibition. The relationship between initial TSAT and C_{max} of iron is shown in Figure 4 for the 8 mg/kg dose group.

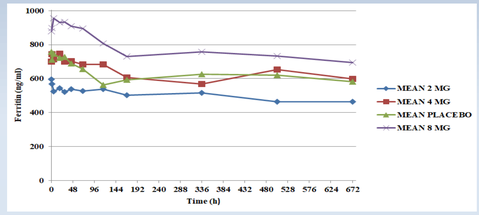

Figure 3: Plasma concentrations versus time profiles of FERRITIN for the three different dose levels and Placebo

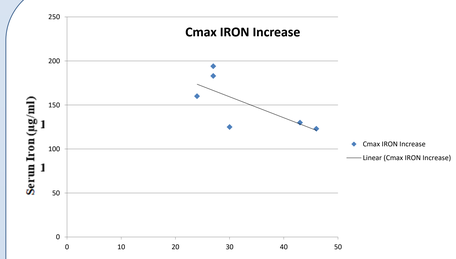

Figure 4 : C_{max} of Iron after Infusion of 8 mg/kg PRS-080#022-DP against Initial TSAT

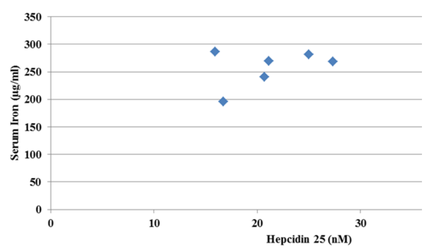

Figure 5 : C_{max} of Iron after Infusion of 8 mg/kg PRS-080#022-DP against Initial hepcidin values

Administration of PRS-080#022-DP resulted in a complete inhibition of free hepcidin shortly after intravenous infusion. Further, there was no evidence across all dose groups that the increase in serum iron exposure is dependent on the initial plasma hepcidin value. This is shown in Figure 5 for the 8 mg/kg dose group.

Pharmacokinetics and Safety Mean plasma concentrations of Total and Free PRS-080#022-DP show a dose-dependent increase after administration of 2, 4 and 8 mg/kg PRS-080#022-DP. T_{max} of Total and Free PRS-080#22-DP occur at about 1 to 1.085 hours (median). (Figure 6)

PRS-080#022 was safe and well tolerated. The only reported serious adverse event (worsening of dry gangrene) after active treatment (2 mg/kg bw dose) was assessed as not related to PRS-080#022-DP by the investigator. No injection site reactions and no dose-dependent increase of AEs was observed within the 3 dose groups.

Conclusion The excellent safety profile and the confirmed activity of PRS-080#022-DP on iron metabolism observed in anemic dialysis dependent end-stage chronic kidney disease patients warrant further investigation of PRS-080#022-DP.

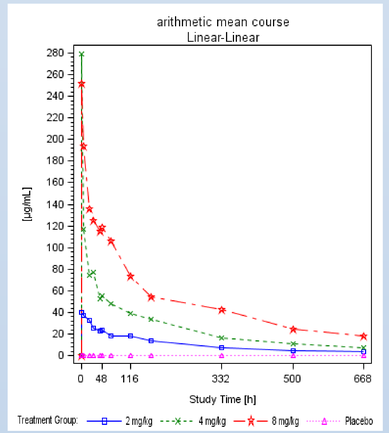

Figure 6: Mean plasma concentration of Total PRS-080#022-DP

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.
[2] 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: 54th ERA-EDTA 2017 congress Madrid, June 3-6, 2017.

Financial disclosure statement
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Topic: Chronic renal failure