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

Lutz Renders, MD¹; Ming Wen, MD²; Frank Dellanna, MD²; Heinrichs, Sven, MD²; Klemens Budde, MD³; Christian Rosenberger, MD³; Christiane Erley, MD³; Birgit Bader, MD³; Claudia Sommerer, MD³; Schäfer, Matthias, MD²; Werner Feuerer, MD²; Edgar Fenzl, MD³; Rachel van Swelm, PhD³; Dorine Swinkels, MD PhD³; Klaus Kutz, MD³; Louis Matis, MD³⁴; Ulrich Moebius, PhD³⁵

¹Klinikum Rechts der Isar, Department Nephrology, Munich, Germany; ²DaVita Düsseldorf, Germany; ³Chanté Berlin, Germany; ⁴St. Joseph Krankenhaus, Berlin, Germany; ⁵University Hospital Heidelberg, Germany; ⁶NVusian Pharma Services, Neu-Ulm, Germany; ⁷FGK Clinical Research, Munich, Germany; ⁸Radboud University Medical Center, Nijmegen, The Netherlands; ⁹AccelPharm, Basel, Switzerland; ¹⁰Pieris Pharmaceuticals, Inc., Bozeman, Montana; ¹¹Pieris Pharmaceuticals, Inc., Freising, Germany.

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 design: 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 month 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.

Pharmacodynamics

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

Table 1: Baseline patient characteristics

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.

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. Tmax of Total and Free PRS-080#022-DP occur at about 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.

Reference

[1] Phase I study investigating the safety, tolerability, Pharmacokinetics and Pharmacodynamics Activity of the Hepcidin Antagonist PRS-080#022. Results from a Randomized, Placebo Controlled, Double-Blind Study Following Single Administration in Healthy Subjects. ASAIO 2015 meeting & exposition, Dec. 3-5, 2015.
[2] A phase Ib study investigating the safety, tolerability, Pharmacokinetics and Pharmacodynamics Activity of the hepcidin antagonist PRS-080#022 is chronic kidney disease patients undergoing hemodialysis. 54th ERA-EDTA 2017 congress Madrid, June 3-6, 2017.

Financial disclosure statement

L Mats et al. Moebius are co-worker of Pieris Pharmaceuticals, Inc., all other authors have financial relationships with Pieris Pharmaceuticals, Inc. and received payment for study participation.

Topic: Chronic renal failure

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

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

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.