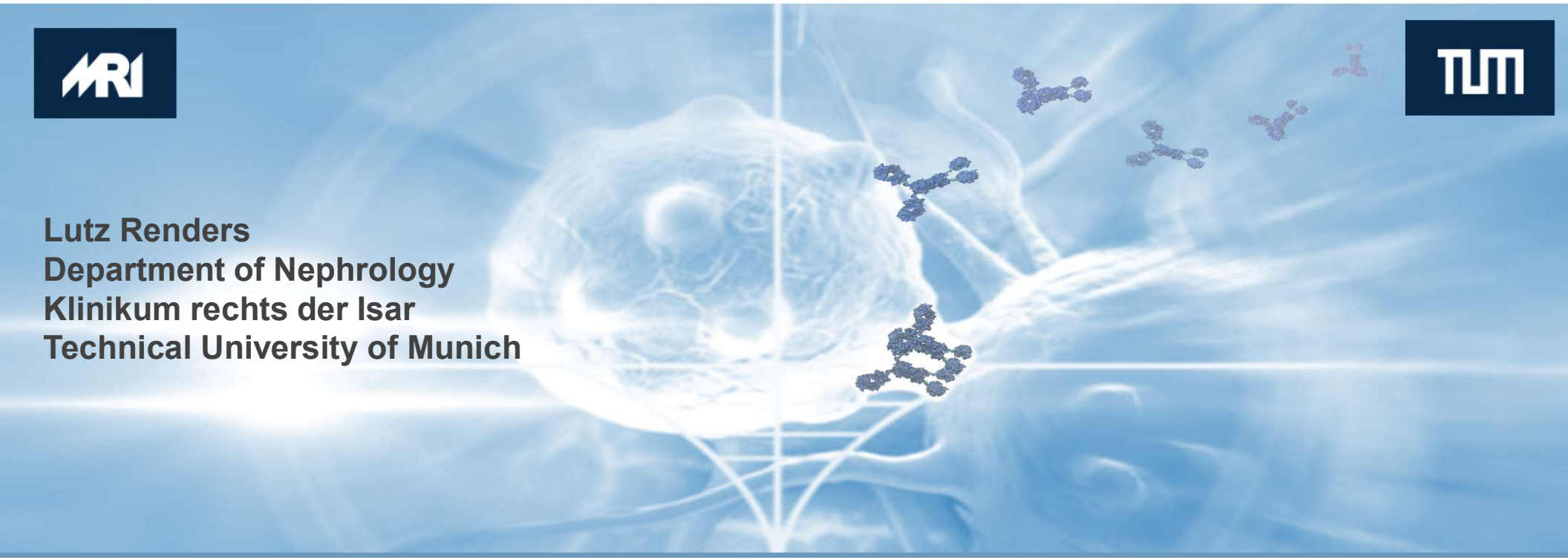

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A PHASE 2A STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF REPEATED ADMINISTRATIONS OF THE HEPCIDIN ANTAGONIST PRS-080 OVER 4 WEEKS IN ANEMIC CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS

Lutz Renders, Frank Dellanna, František Švára, Jitka Řehořová, Ondřej Viklický, Ming Wen, Matthias Braunisch, Karoline Meurer, Anne Maschek, Goran Martić, Kayti Aviano, Louis Matis, Ingmar Bruns

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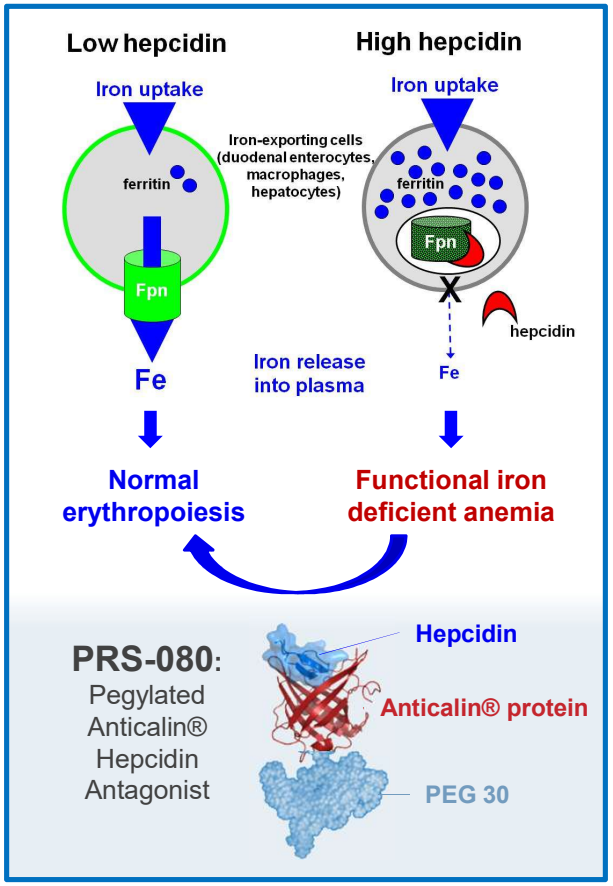
Antagonizing Elevated Hepcidin Levels in Anemias of Chronic Disease

- **Hepcidin is elevated in multiple chronic inflammatory conditions associated with anemia**
  - Infections, cancer, rheumatoid arthritis (RA), chronic kidney disease (CKD)
- **Iron metabolism is regulated by hepcidin/ferroportin**
  - Hepcidin inhibits iron export from cells by blocking ferroportin
  - Excess hepcidin is the root cause of hypoferremia and iron-restricted reduction of erythropoiesis seen in anemia of chronic disease (ACD)
  - Hepcidin inhibits erythroid colony formation at reduced erythropoietin concentrations
- **Inhibition of hepcidin to treat functional iron deficient erythropoiesis and anemia is expected to**
  - Increase availability of internal iron sources
  - Increase erythropoietin stimulating agents (ESA) responsiveness allowing reduction of ESA doses
  - Prevent iron overload from exogenous administration
  - Increase and stabilize hemoglobin (Hb) levels



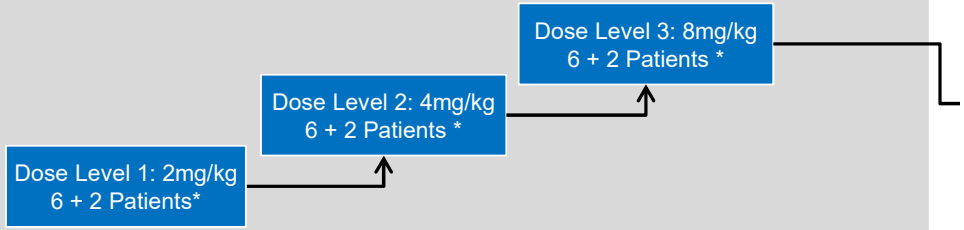
PRS-080: Phase 1b & Phase 2a Outline

Patient Population: ESRD/CKD patients on dialysis

- Ferritin ≥ 300 ng/ml
- Hepcidin 5-75 nM

Phase 1b: Single Administration

- Hb 9 – 12 g/dL
- TSAT ≤ 40%



- Safety
- Pharmacokinetics
- Hepcidin neutralization
- Iron / TSAT

*: 6 + 2 Patients: 6 active and 2 placebo

PRS-080: Phase 1b & Phase 2a (P2a) Outline

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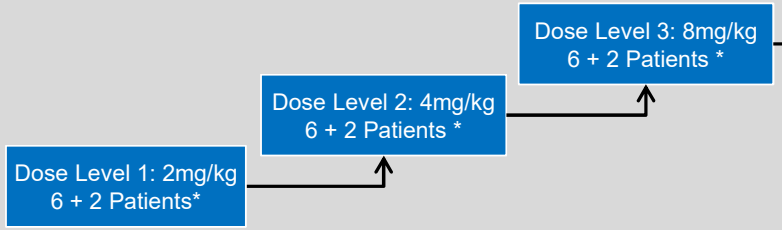

- Safety
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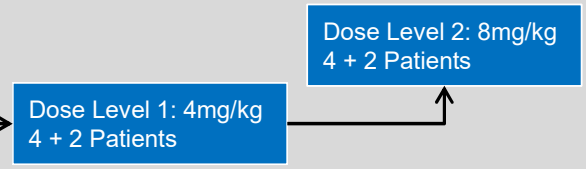
- Iron / TSAT

*: 6 + 2 Patients: 6 active and 2 placebo

Phase 2a: Repeated Administration

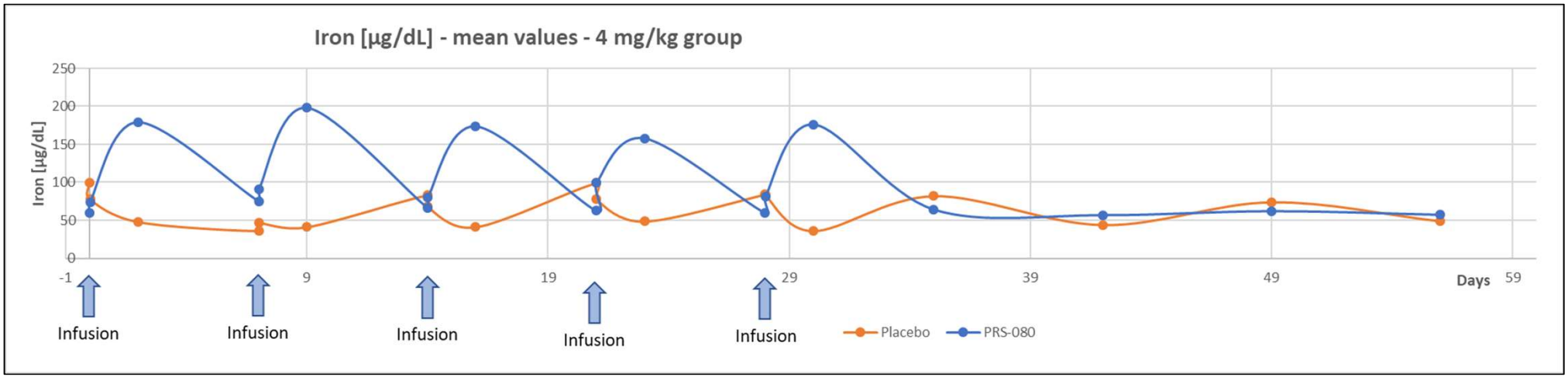
- Hb < 10.5 g/dL
- TSAT ≤ 30%



5 administrations (1x/week, for 4 weeks)

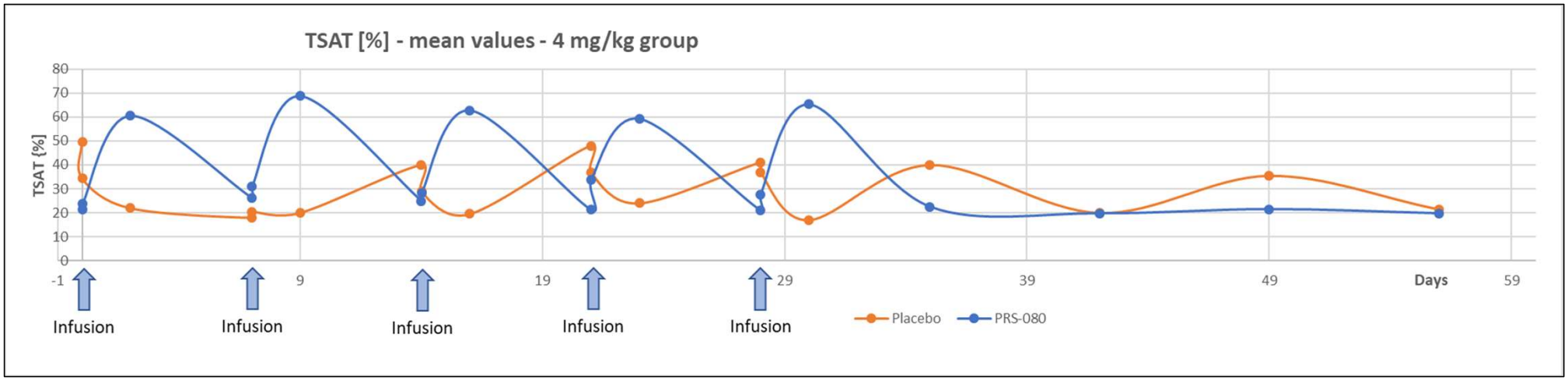
- Safety
- Pharmacokinetics
- Hepcidin neutralization
- Iron / TSAT
- **Hb**
- Reticulocyte Hb (CHr)

P2a: Mean Iron Values of 4 mg/kg Patient Group



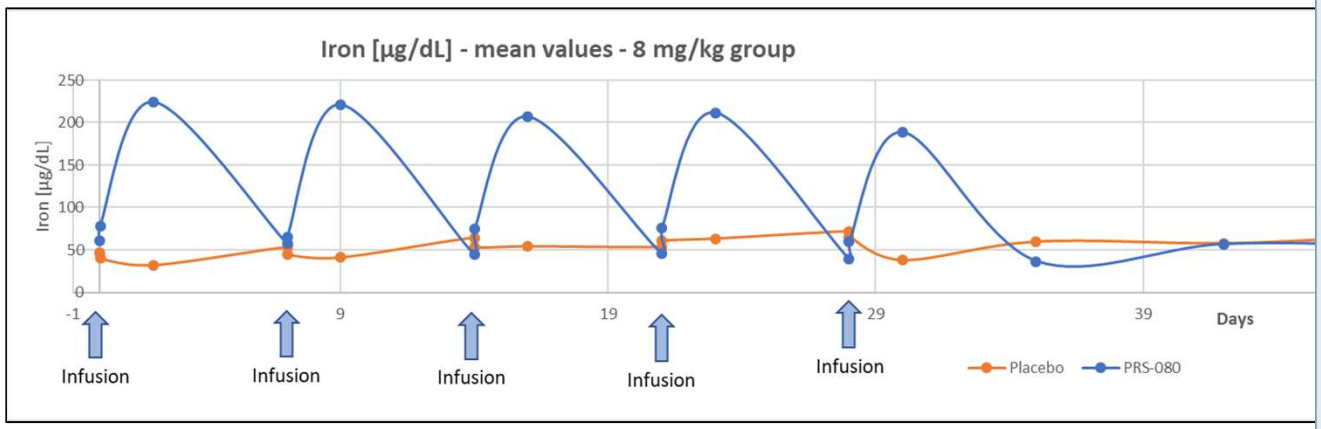
- Iron response and mobilization in serum iron after each dose of PRS-080 in drug-treated patients
- No iron response in placebo-treated patients

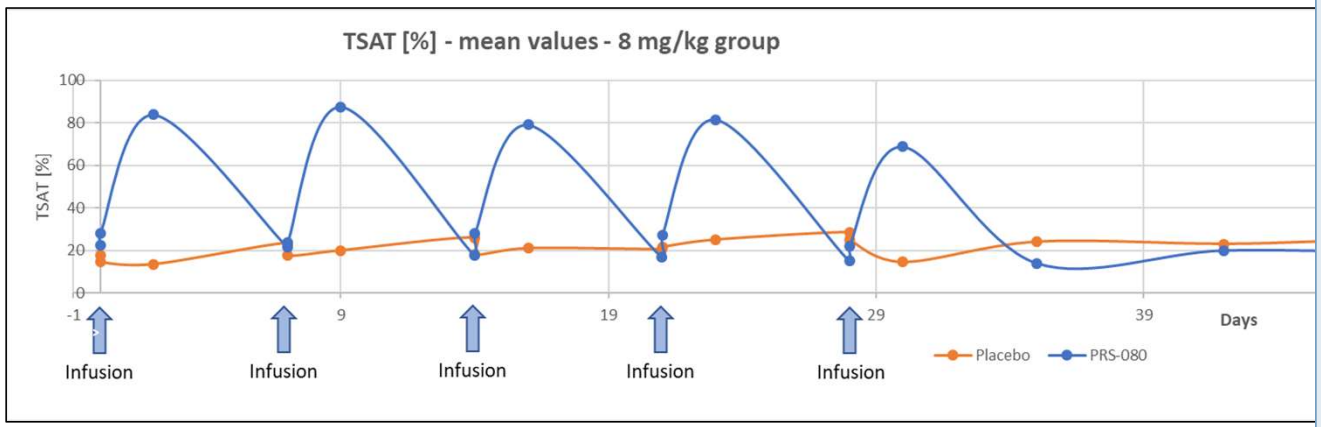
P2a: Mean TSAT% Values of 4 mg/kg Patient Group



- Mobilization of iron in TSAT after each dose of PRS-080 in drug-treated patients
- No iron response in placebo-treated patients

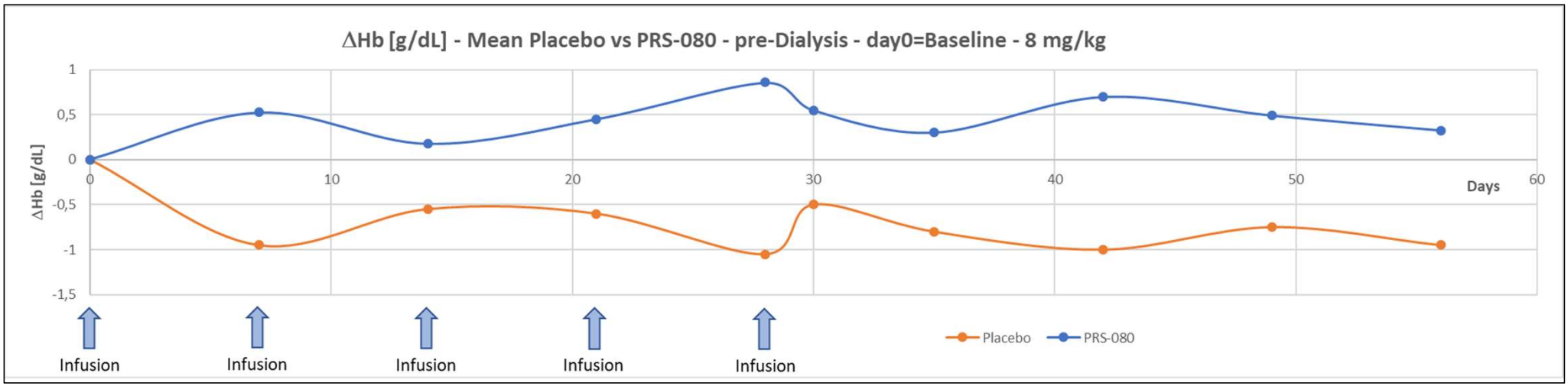
P2a: Mean Iron and TSAT% Values of 8 mg/kg Patient Group





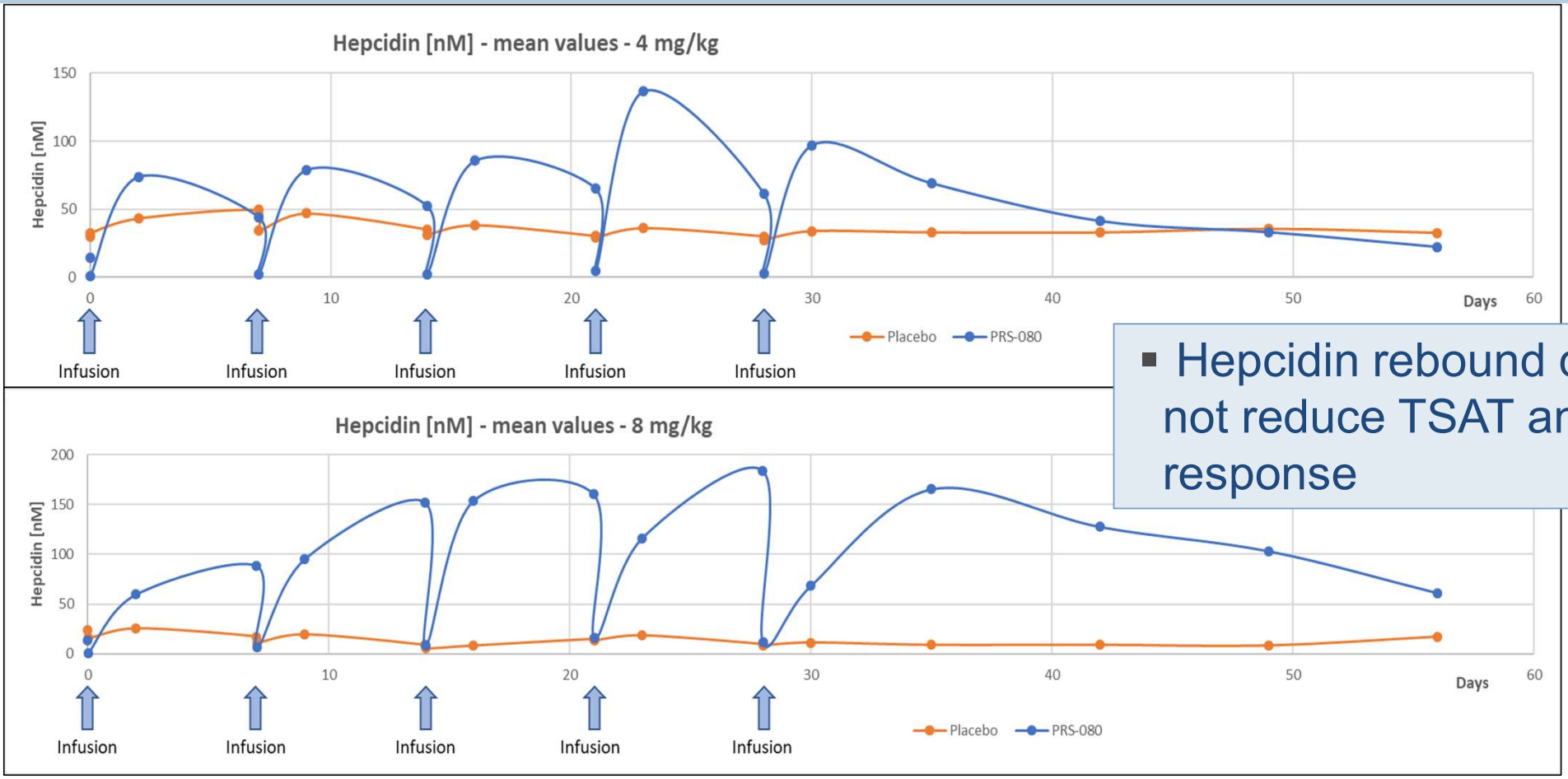
- Iron response and mobilization in both serum iron and TSAT after each dose of PRS-080 in drug-treated patients
- Slightly higher peak iron response in the 8 mg/kg treatment group vs 4 mg/kg group
- No iron response in placebo-treated patients

P2a: At 8mg/kg, Preliminary Evidence of an Increase in Hb With PRS-080 Treatment Compared to Placebo Group



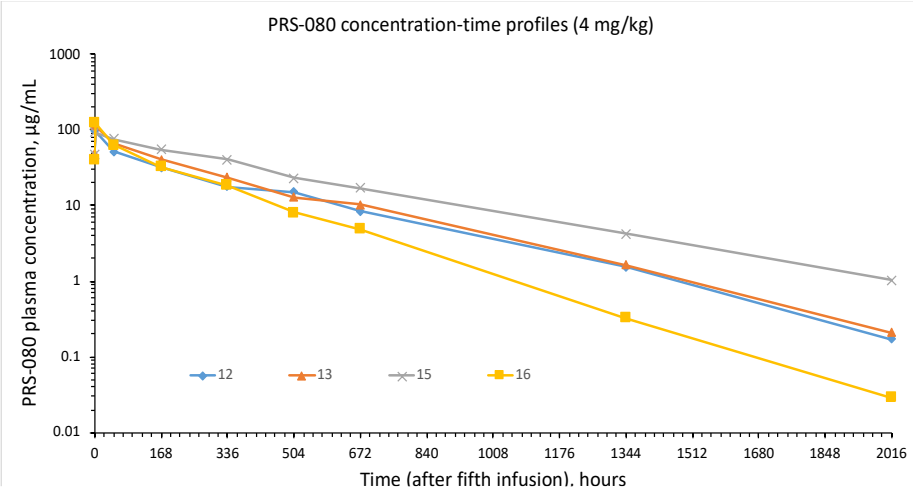
- Both Placebo and PRS-080 groups with no iron administration during study
- Modest increase in Hb in the treated patient group
- Decline in the placebo group, possibly related to discontinuation of parenteral iron administration

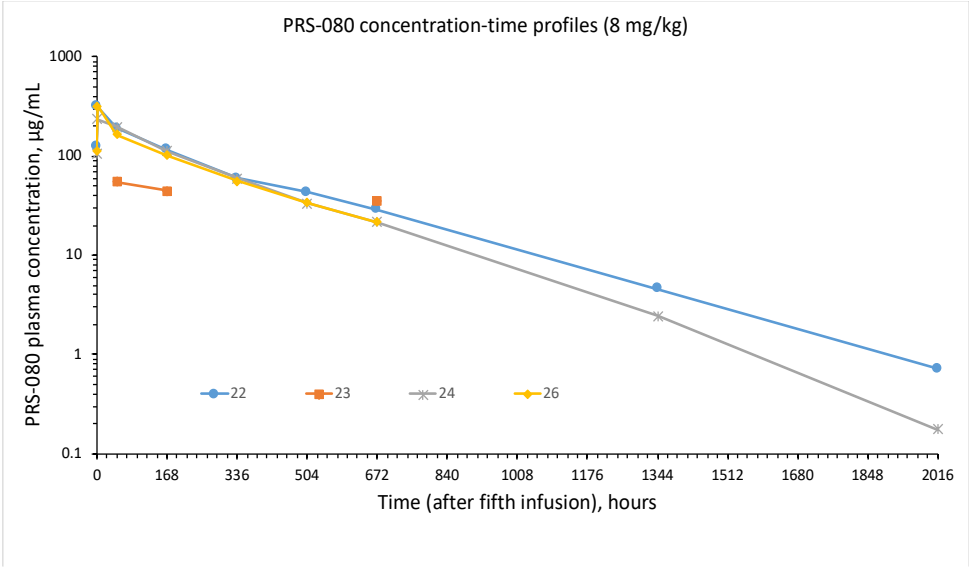
P2a: Hepcidin Analysis – Dose-Dependent Rebound



- Hepcidin rebound does not reduce TSAT and iron response

P2a: PRS-080 half-life in CKD patients





Pharmacokinetics

- 4 patients (Subject number 12, 13, 15 and 16) received 4 mg/kg PRS-080
- 4 patients (Subject number 22, 23, 24 and 26) received 8 mg/kg PRS-080
- Blood samples for PRS-080 determination were collected up to 84 days (approximately 2016 hours) after administration of fifth and last dose.
- PRS-080 terminal phase half-life was calculated by non-compartmental method using nominal (planned) time points and preliminary values are provided

PRS-080 half-life (n = 7) *

- Geometric mean (%CV) PRS-080 half-life was estimated to be 237 hours (20%)

* Subject 23 provided intermittent PK samples and is not included in half-life calculation

- PRS-080 half-life estimate was consistent with previously reported values in Phase 1b study
- PRS-080 with sufficient half-life and possible prolongation by renal insufficiency
- No accumulation of PRS-080

Phase 2a Multidose Study of the Hepcidin Inhibitor PRS-080 in Anemic Chronic Kidney Disease Patients Undergoing Hemodialysis: Summary

- PRS-080 was safe and well tolerated at both 4 mg/kg and 8 mg/kg treatment dose levels (data not shown)
- No treatment-related adverse events (AEs) or serious adverse events (SAEs) observed (data not shown)
- Robust iron mobilization with increases in both serum iron and TSAT
- Peak iron concentrations were higher in the 8 mg/kg treatment group
- No clear difference in Hb values between placebo and PRS-080 in 4 mg/kg treatment group over the course of treatment (data not shown)
- Preliminary evidence of Hb response with separation of Hb values between placebo and PRS-080 shown in the 8 mg/kg treatment group during the treatment period
  - Apparent Hb increase in drug-treated patients, even after discontinuation of iron treatment
  - Hb decline in placebo patients, potentially related to the withdrawal of iron treatment
- Half-life suggests adequate dosing schedule, reduced clearance possibly due to impaired renal function but no accumulation effects