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

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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%

- Dose Level 1: 2mg/kg
  6 + 2 Patients*

- Dose Level 2: 4mg/kg
  6 + 2 Patients*

- Dose Level 3: 8mg/kg
  6 + 2 Patients*

- Safety
- Pharmacokinetics
- Hepcidin neutralization
- Iron / TSAT

*: 6 + 2 Patients: 6 active and 2 placebo
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### Phase 1b: Single Administration

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  - 6 + 2 Patients *
- Dose Level 2: 4mg/kg
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- Dose Level 3: 8mg/kg
  - 6 + 2 Patients *

- Safety
- Pharmacokinetics
- Hepcidin neutralization
- Iron / TSAT

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

### Phase 2a: Repeated Administration

- Dose Level 1: 4mg/kg
  - 4 + 2 Patients
- Dose Level 2: 8mg/kg
  - 4 + 2 Patients

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
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