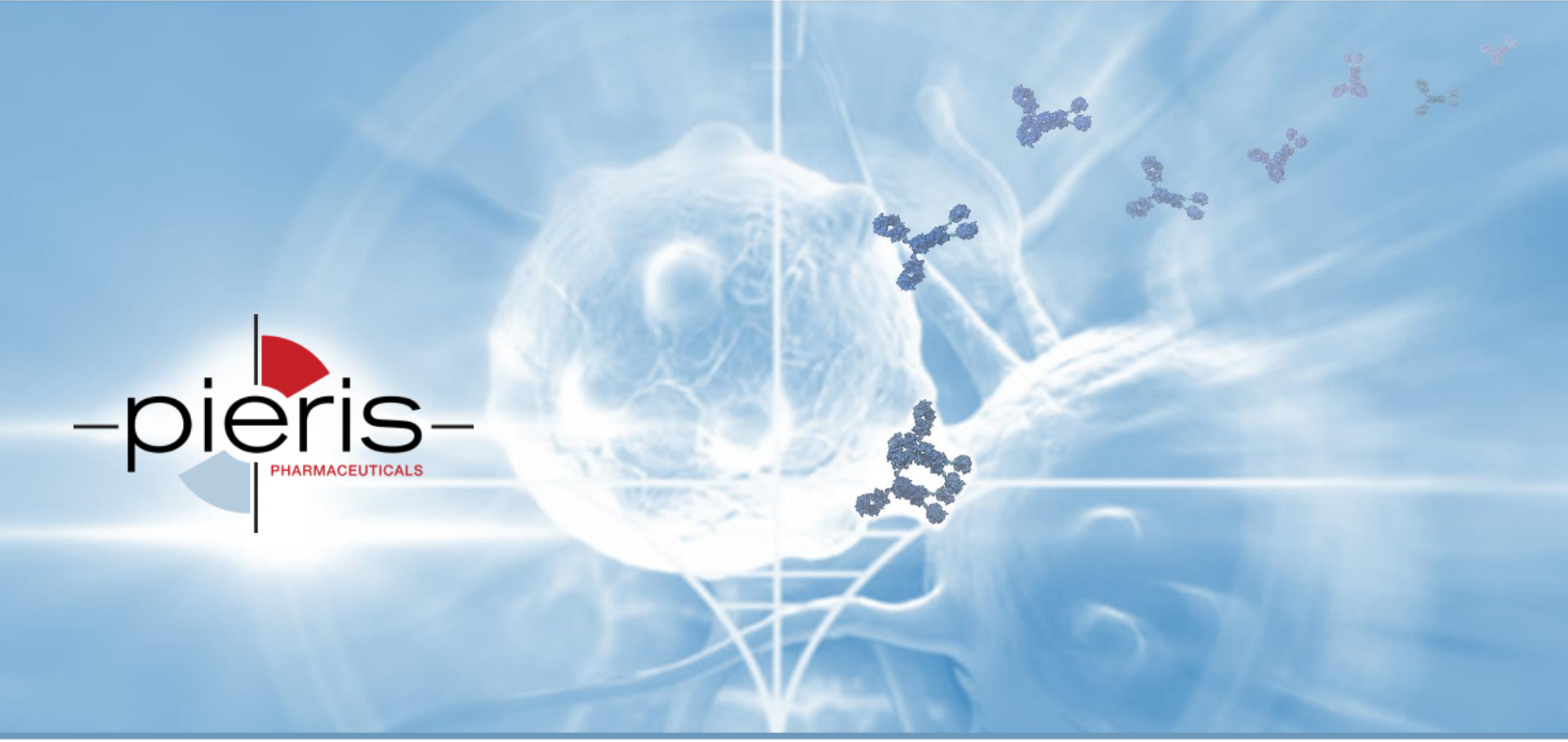

A Phase I Study Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Activity of the Hepcidin Antagonist PRS-080#022. Results from a Randomized, Placebo Controlled, Double-Blind Study Following Single Administration to Healthy Subjects

December 07, 2015

57th Annual Meeting of the American Society of Hematology, Orlando, FL

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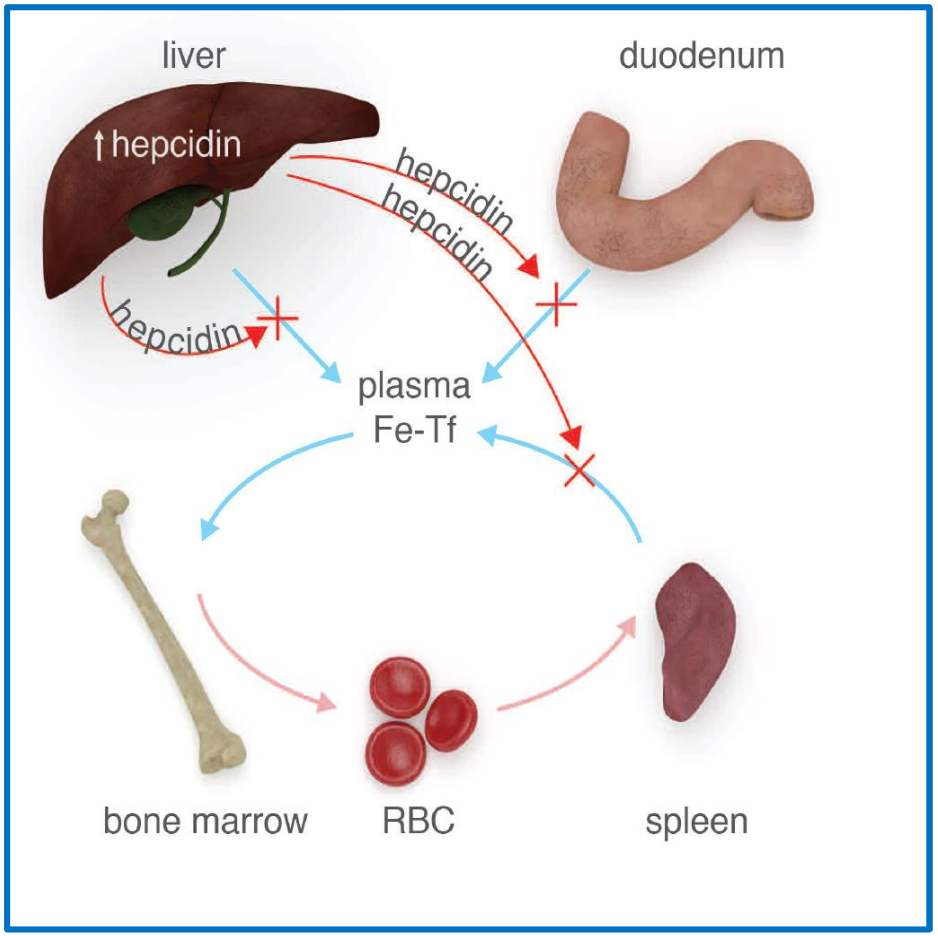
Hepcidin Plays a Central Role in Iron Metabolism

Hepcidin is a 25 amino acid peptide hormone that serves as a **key regulator of iron metabolism** by inhibiting iron entry into plasma from the three main sources of iron:

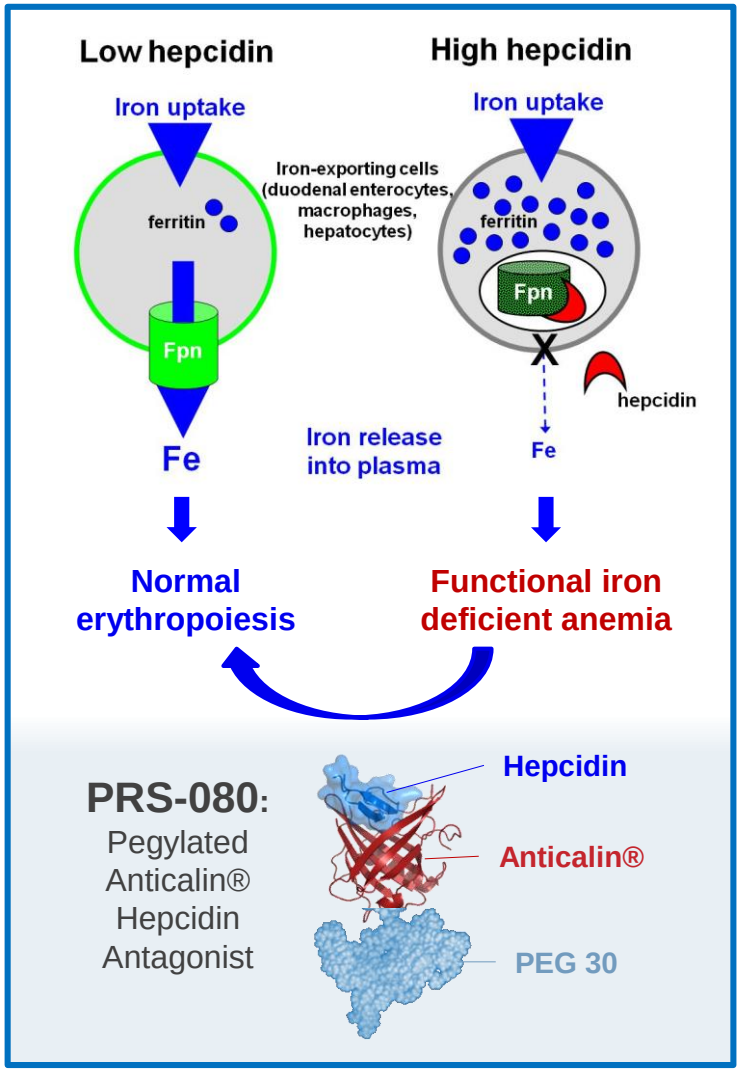
- Dietary absorption in the duodenum
- Release of recycled iron from macrophages
- Release of stored iron from hepatocytes



Haematologica 2013 98:11

Antagonizing Elevated Hepcidin Levels in Anemias of Chronic Disease (ACD)

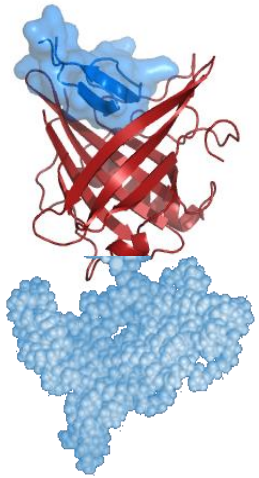
- **Hepcidin elevated in multiple chronic inflammatory conditions associated with anemia**
  - Infections, cancer, RA, chronic kidney disease (CKD)
- **Iron metabolism regulated by hepcidin/ferroportin**
  - Hepcidin inhibits iron export from cells by blocking ferroportin
  - Excess hepcidin is the root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



PRS-080 is a Highly Potent Anticalin® Hepcidin Antagonist

- **Anticalins®** – derived from human lipocalins – are a **novel class of therapeutic binding proteins** (MW 16-20kD), that demonstrate high target affinity and exquisite specificity

- **PRS-080 is a pegylated Anticalin®** protein derived from the human lipocalin NGAL, that acts as a **potent hepcidin antagonist**
  - 50 pM affinity for hepcidin
  - Produced by bacterial expression in E. coli
  - Inhibits hepcidin-induced ferroportin internalization
  - Optimized plasma half life by conjugation to PEG 30
  - No adverse effects in non-human primate toxicity studies



PRS-080 Has Been Investigated in Phase I in Healthy Subjects

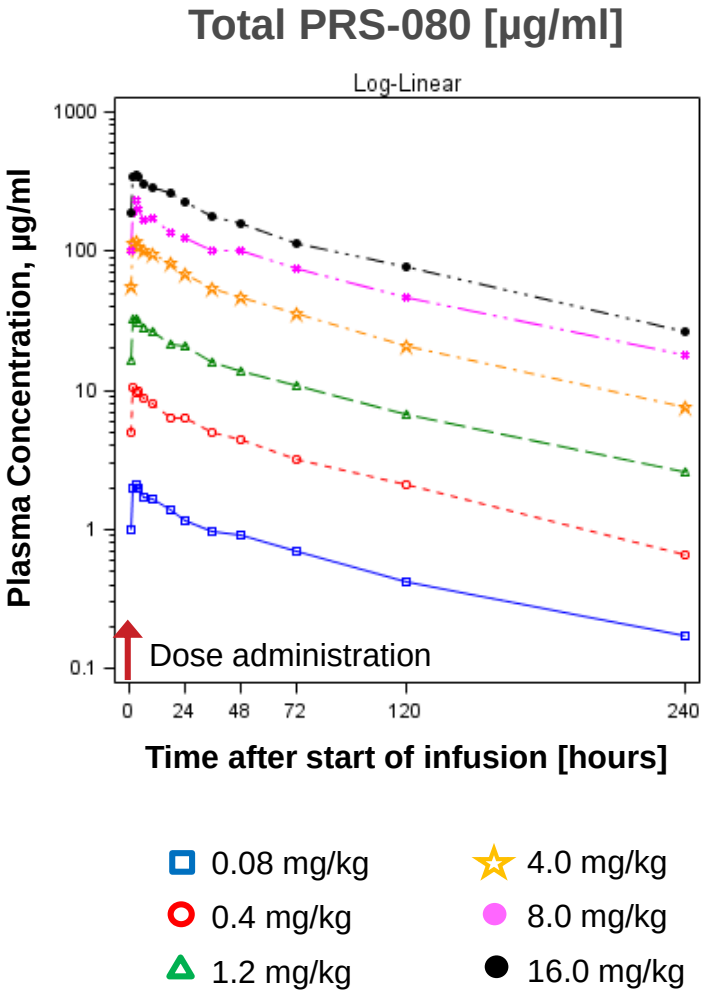
- Single dose escalating study in healthy male subjects, n=48
  - Randomized, double blinded, placebo controlled study
- 6 dose cohorts
  - 0.08, 0.4, 1.2, 4.0, 8.0, 16.0 mg/kg (based on API without PEG)
  - I.V. infusion over 2 hours
  - 6 subjects receiving PRS-080, 2 subjects receiving placebo per cohort
- Endpoints
  - Safety and maximal tolerated dose
  - Pharmacokinetics
  - Pharmacodynamics (serum iron, transferrin saturation)
  - Hepcidin plasma concentrations
  - Immunogenicity

PRS-080 Was Well Tolerated in Healthy Subjects

- No serious Adverse Events (AE)
- 39 treatment emergent AEs (TEAE) in 22 subjects
  - 30 mild TEAEs
  - 9 moderate TEAEs
- Headache was most common TEAE (10 subjects)
- Otherwise, no association of AEs to specific organs
- No apparent correlation between dose and number of TEAEs
- No hypersensitivity, no infusion reactions
- Vital signs and ECG without changes
- No cytokine release upon PRS-080 administration
  - IFN-γ, IL-1β, IL-6 and TNF-α

PRS-080 Shows Dose Proportional Pharmacokinetics

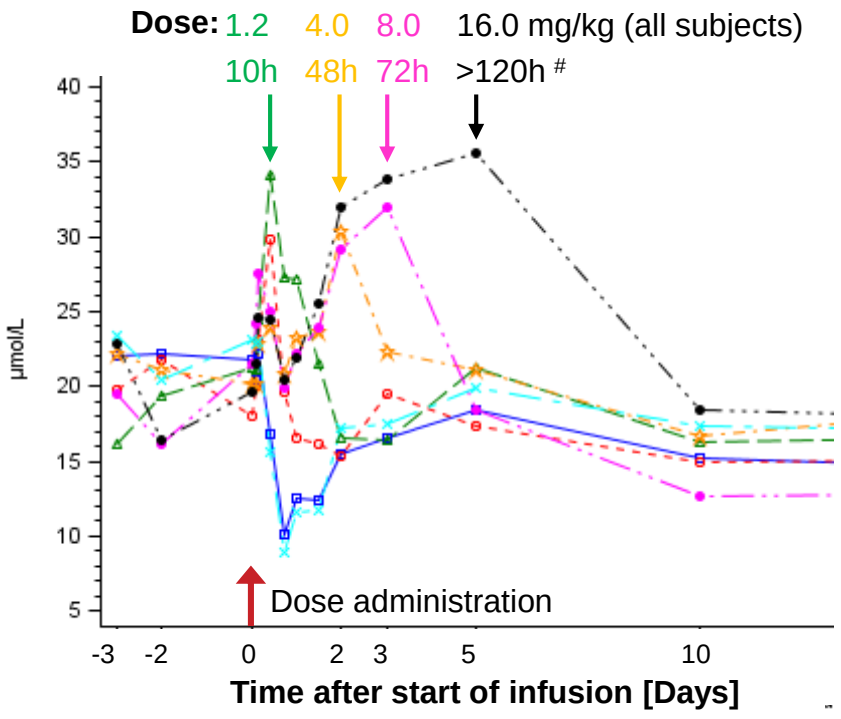
- **Total PRS-080**
  - Dose proportional C_{max} and AUC
  - T_{max} at around 1h after end of infusion
  - $T_{1/2}$ at 64 to 81 hours (geometric mean)
    - 71 to 81 hours, arithmetic mean
  - Small volume of distribution (48 - 65 ml/kg)
    - Consistent with distribution to blood volume
- **Free PRS-080**
  - C_{max} and AUC lower compared to total PRS-080
  - $T_{1/2}$ at 40 to 62 hours
    - Consistent with “consumption” of free PRS-080 by hepcidin binding



PRS-080 Shows Dose-Dependent Effects

Increased Duration & AUC of Elevated Serum Iron Concentrations

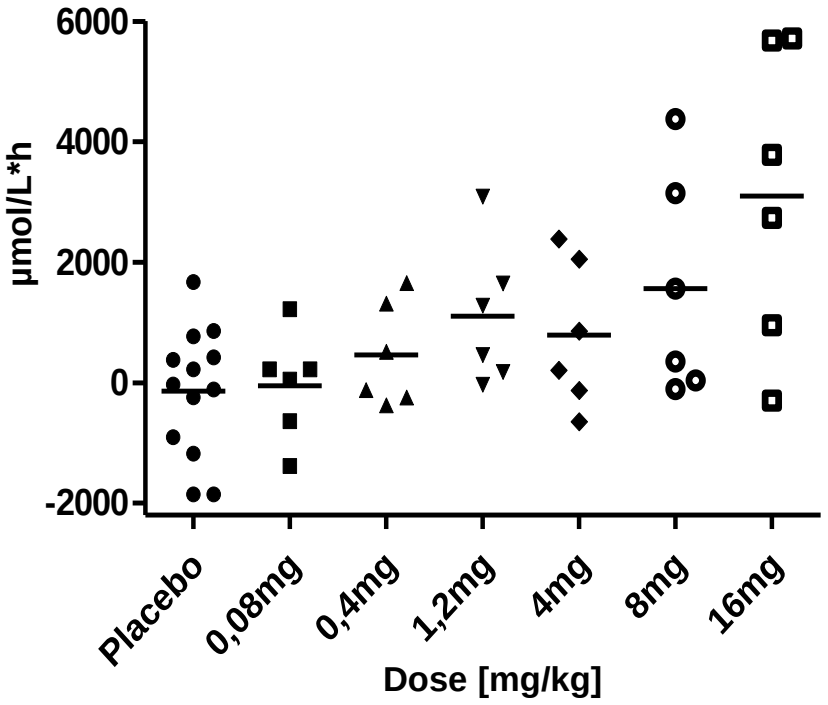
Mean Iron Concentrations



Time point of peak iron conc. (hrs after start of infusion)

Area Under the Curve

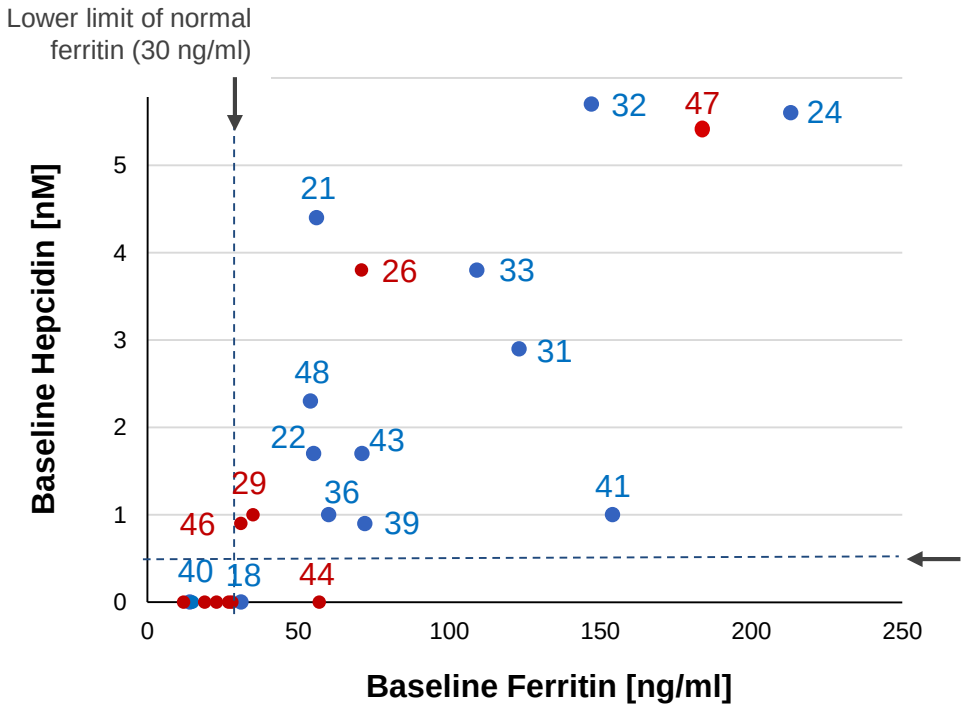
Iron concentration over baseline
Individual subjects and mean*



* Mean placebo value subtracted

PRS-080 Induced Iron Response is Correlated to Baseline Ferritin & Hepcidin

- Serum iron response generally observed in subjects with normal ferritin (> 30 ng/ml) and detectable hepcidin (> 0.5 nM) at baseline
- Subjects of dose cohorts 1.2 to 16.0 mg/kg shown below
  - Subjects achieving iron response (> 34.5 µM = Fe ↑)
  - Subjects without iron response (< 34.5 µM = Fe →)



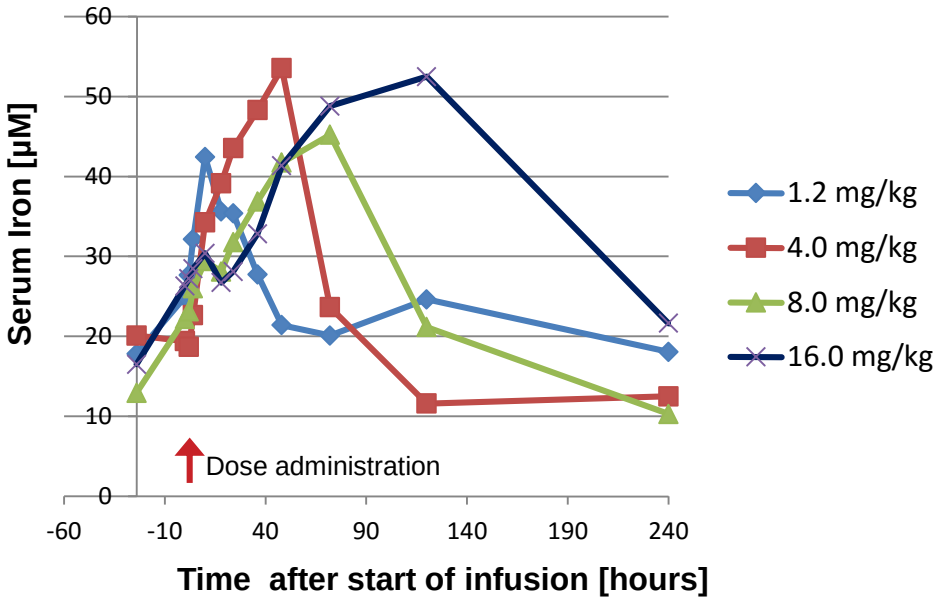
	Ferritin > 30 ng/ml Hepcidin >0.5 nM	No. of subjects	
		Fe ↑	Fe →
PRS-080 [1.2–16 mg/kg]	+	**11**	4
	-	2	**7**
Placebo	+	1	**9**
	-	1	1

Duration of Iron Response After PRS-080 Administration is Dose-Dependent

- Duration of response increases with dose
- Individual peak serum iron concentrations are independent of dose

Mean Iron Concentrations

Subjects achieving iron response > 34.5 µM



Time to Peak
Duration of Response
Peak Iron Concentration

Dose [mg/kg]	1.2	4.0	8.0	16.0
Time to peak iron concentration	10h	48h	72h	120h
Duration of iron response*	25h	64h	94h	185h
Peak serum iron concentration [µM]	42.5	53.6	45.2	52.2

* Estimated time point where serum iron falls <34.5 µM

PRS-080 Shows Favorable Safety Profile/ Confirms Mechanism of Action in Phase 1

- PRS-080 was **well tolerated** in healthy subjects
- **Pharmacokinetics as expected**: $T_{1/2}$ ~ 3 days
- Immediate **dose-dependent decrease in circulating hepcidin**
- **Dose-dependent duration of serum iron and TSAT responses**
  - From 24 hours up to >120 hours
  - Predominantly observed in subjects with normal ferritin (>30 ng/ml) and detectable hepcidin (>0.5 nM) at baseline
    - Sufficient tissue iron stores and target expression
  - Robust responses at doses of 1.2 mg/kg and above, with **statistically significant increase in total serum iron** relative to placebo (p = .005)
- **No risk of immunogenicity observed**
- **Data support further investigation of PRS-080 in patients with ACD**

Next Steps: Phase Ib/IIa Study to Investigate PRS-080 in Anemic CKD5 Patients

Planned Phase Ib/IIa in CKD5 hemodialysis patients

- Ib: Single Ascending dose; Safety, PK and pharmacodynamic activity (iron, TSAT, hepcidin)
- IIa: MAD, 4 week repeated dosing; anemia (Hb) as primary outcome measure

VALIDATED BIOLOGY

Elevated hepcidin levels in CKD patients as cause for anemia

- Restricted iron utilization
- Impaired erythropoiesis
- Anemia despite i.v. iron and high ESA doses

PROMISING INVESTIGATIONAL DRUG

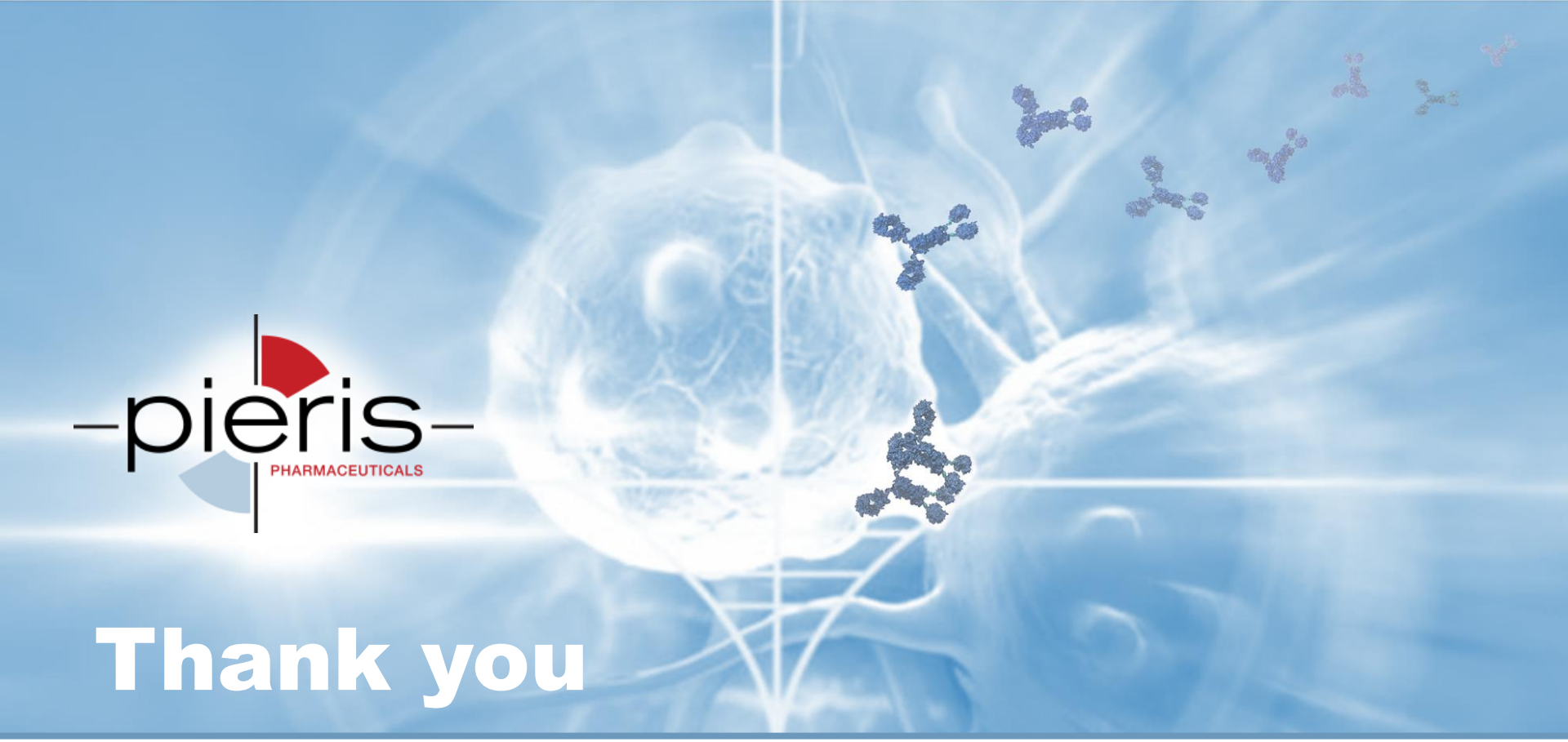
PRS-080 = hepcidin antagonist

- Increases iron mobilization
- Tailored half-life
- Aim to
  - Increase erythropoiesis
  - Reduce ESA and prevent iron overload
  - Reduce anemia

PROMISING CLINICAL ACTIVITY

Phase I study in healthy subjects

- ✓ Excellent safety
- ✓ Pharmacologic activity demonstrated



Thank you

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