S895

HEPCIDIN MIMETIC PTG-300 INDUCES DOSE-RELATED AND SUSTAINED REDUCTIONS IN SERUM IRON AND TRANSFERRIN SATURATION IN HEALTHY SUBJECTS

Andrew Nicholls[1], Jason Lickliter[2], Lucio Tozzi[1], David Liu[1], Richard Shames[1]

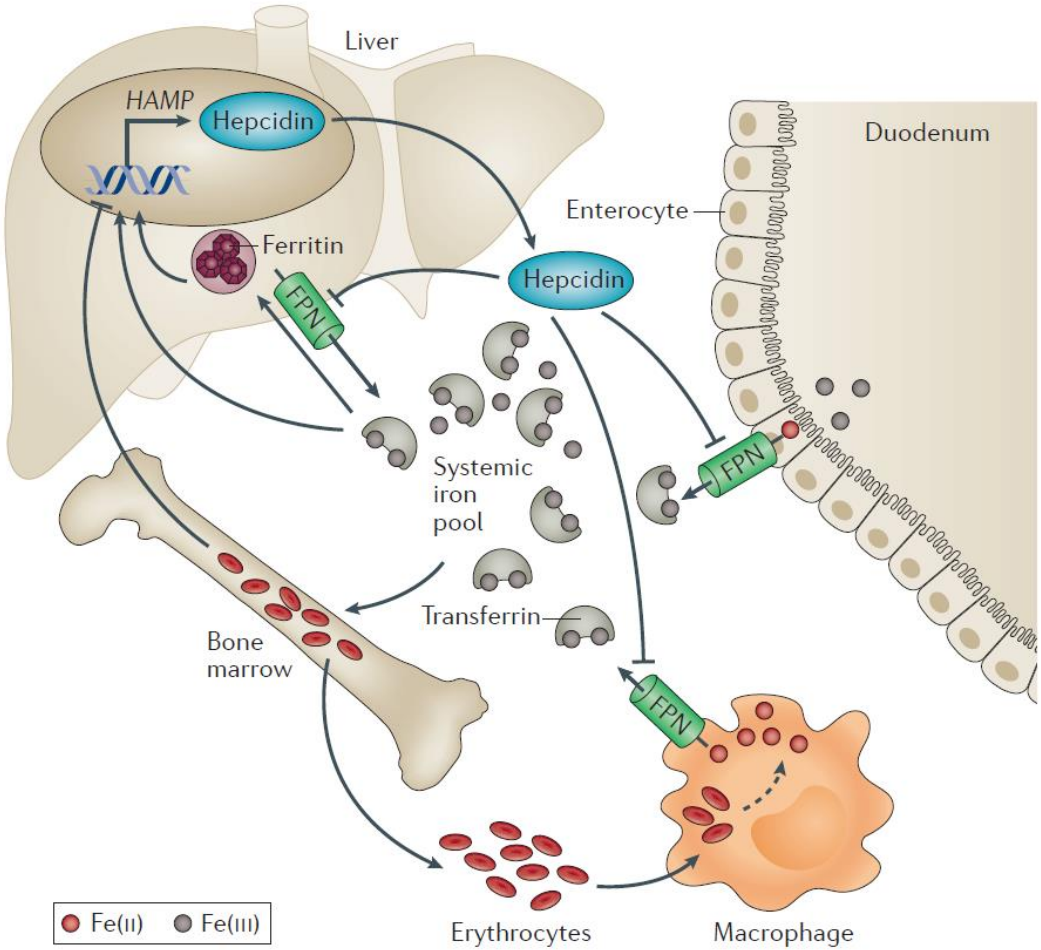
[1]Protagonist Therapeutics. Inc., Newark, CA, USA, [2]Nucleus Network Ltd., Melbourne, Australia

Richard S. Shames, M.D.
Chief Medical Officer
Protagonist Therapeutics, Inc.
EHA June 16, 2018

Financial disclosure

- Dr. Shames is an employee of Protagonist Therapeutics, which sponsored this trial.

Hepcidin is the master regulator of systemic iron metabolism



Crielaard et al, Nature 2017

Hepcidin replacement as a potential therapy for diseases of ineffective erythropoiesis and iron overload

- In conditions of ineffective erythropoiesis, hepcidin levels are suppressed leading to increased iron absorption from the GI tract and iron export from macrophages which is toxic to developing erythrocytes.

- Agents with hepcidin activity may help correct iron distribution abnormalities with beneficial effects on erythropoiesis.

- Hepcidin mimetic has potential to treat multiple conditions:
  - Ineffective erythropoiesis, low hepcidin and iron overload, e.g. β-thalassemia, low risk MDS
  - Primary iron overload, low hepcidin, e.g. hereditary hemochromatosis
  - Exaggerated erythropoiesis, e.g. polycythemia vera

PTG-300 as a potential treatment for ineffective erythropoiesis

- PTG-300, an injectable hepcidin mimetic, is being developed as potential treatment of β-thalassemia.
- Using Protagonist's proprietary peptide technology platform, PTG-300 has been engineered to have specific drug-like properties
  - Potency, efficacy, PK, stability, solubility, and ease of synthesis (COGS)
- Well-tolerated in nonclinical studies; expected effects of exaggerated pharmacology at high doses
- PTG-300 improved anemia and reduced liver iron in a β-thalassemia mouse model (EHA 2018, S-843).

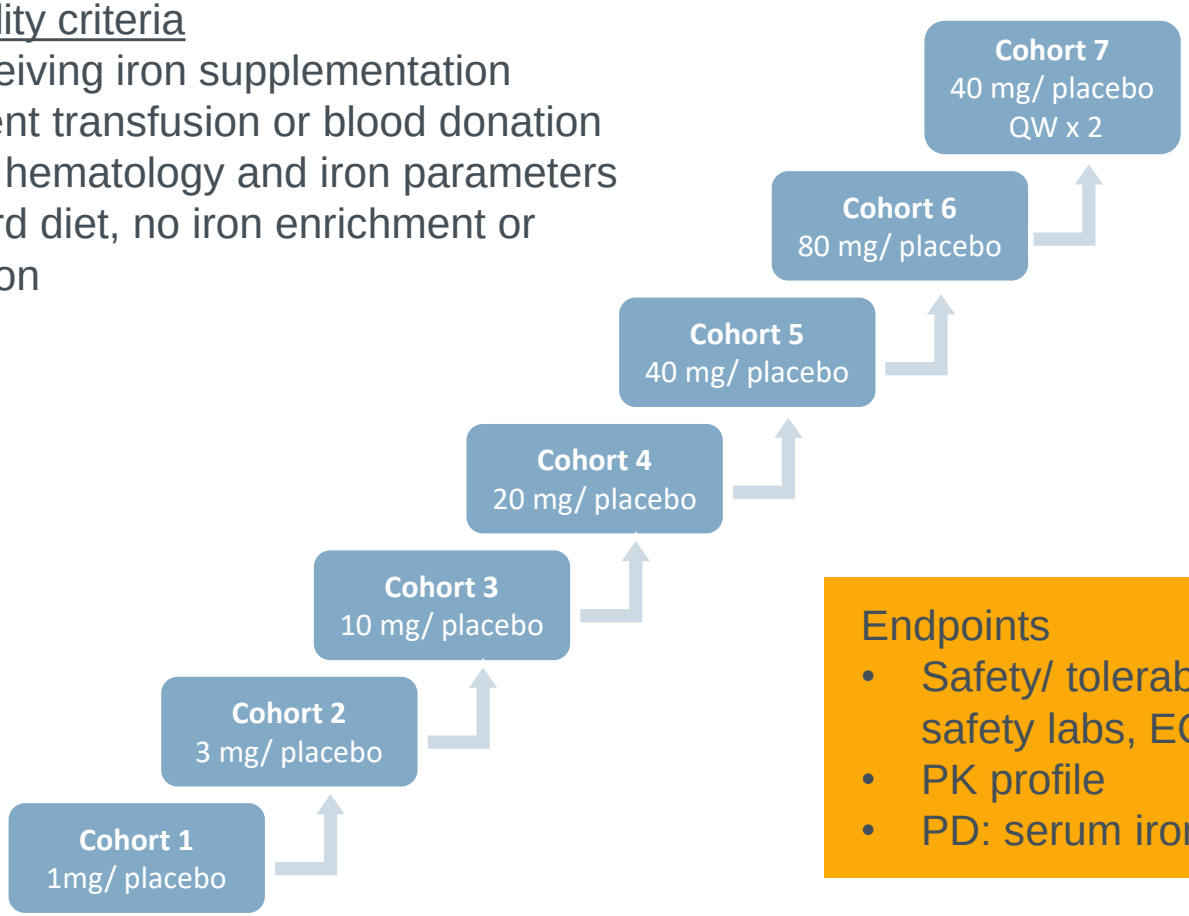
PTG-300: Phase 1 Study in NHVs

Single ascending dose and repeat dose

Randomized, double-blind, placebo controlled Phase 1 Study in NHVs (n = 62)

Key Eligibility criteria

- Not receiving iron supplementation
- No recent transfusion or blood donation
- Normal hematology and iron parameters
- Standard diet, no iron enrichment or restriction



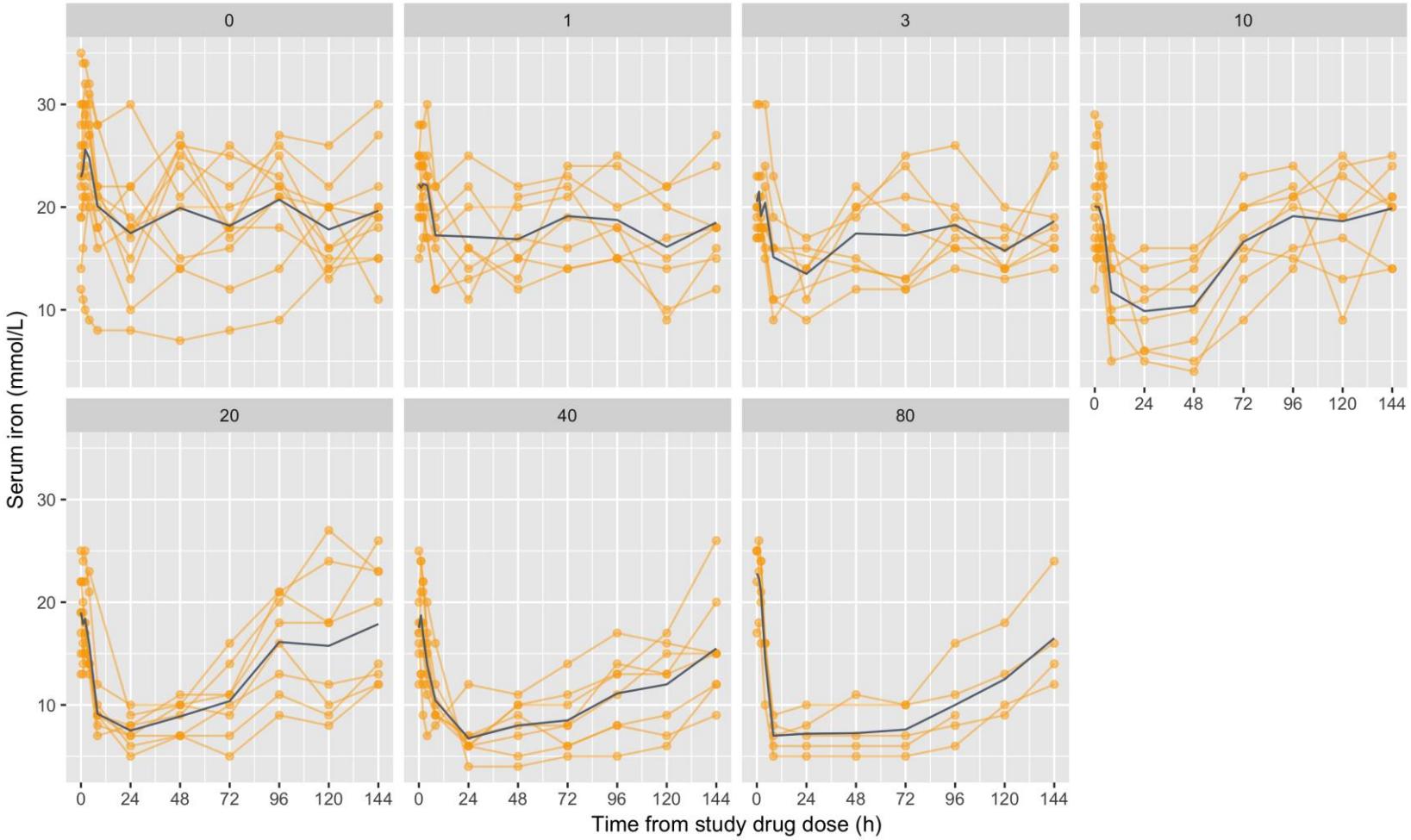
Endpoints

- Safety/ tolerability (AEs/ SAEs, safety labs, ECG, PE)
- PK profile
- PD: serum iron parameters

PTG-300 Induces a Dose-Dependent Reduction in Serum Iron

Maximum Mean Reduction Approximately 65%

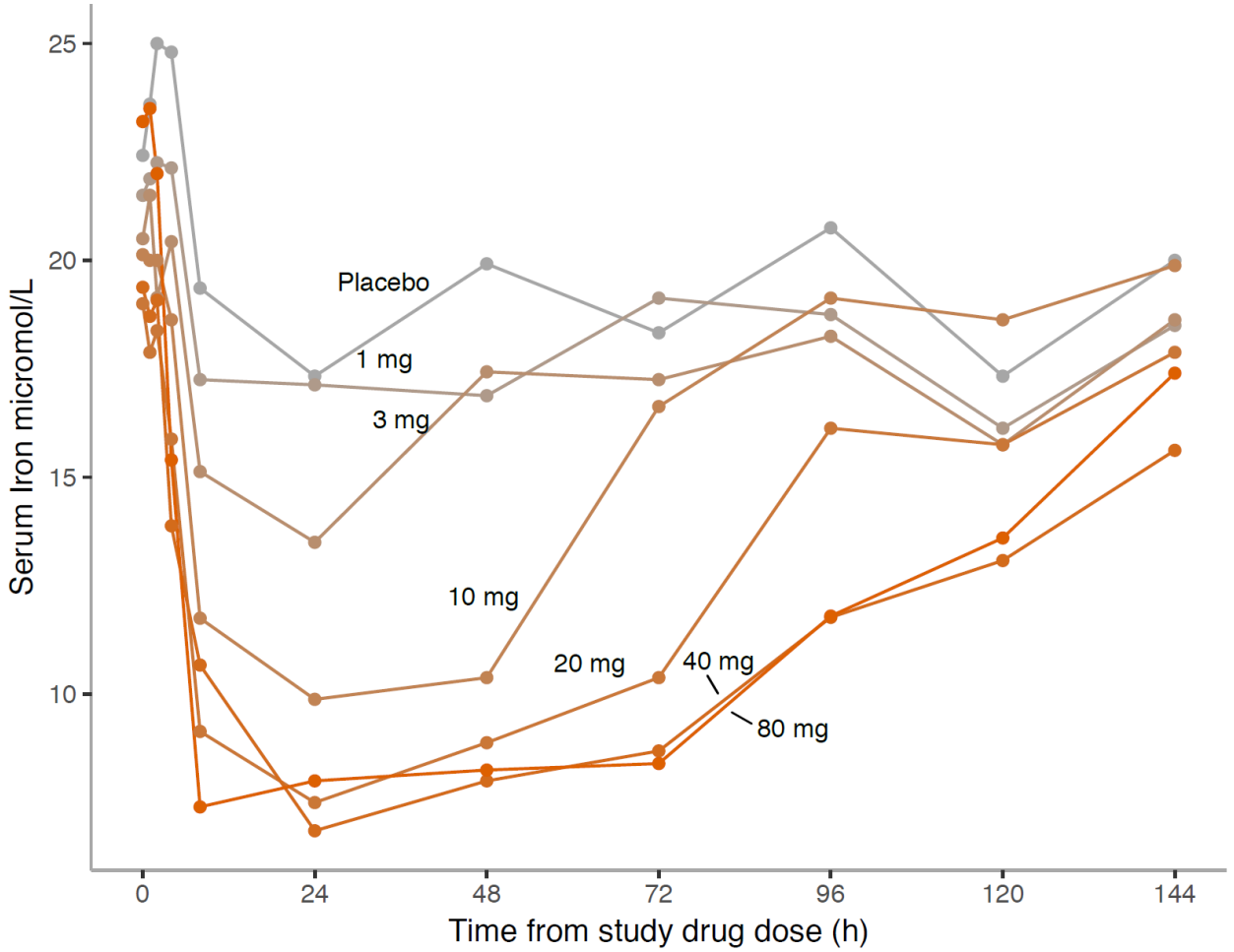
Serum iron - time profiles by single dose level (individual subject and means)



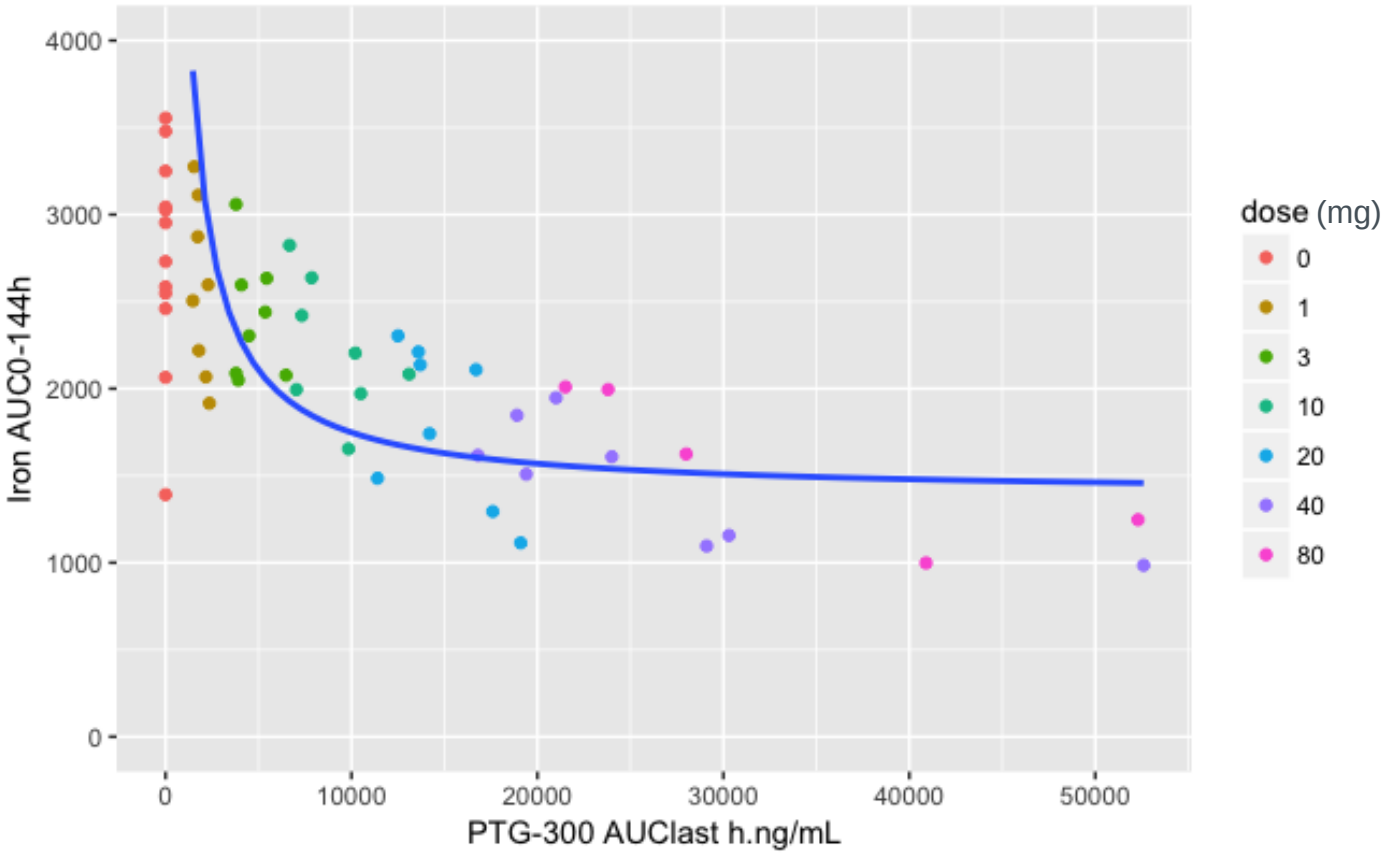
PTG-300 Induces a Dose-Dependent Reduction in Serum Iron

Sustained Reduction >72 hrs at Doses 20 mg or Higher

Mean change in serum iron over time by single dose level



Serum Iron Inversely Correlated with PTG-300 Exposure

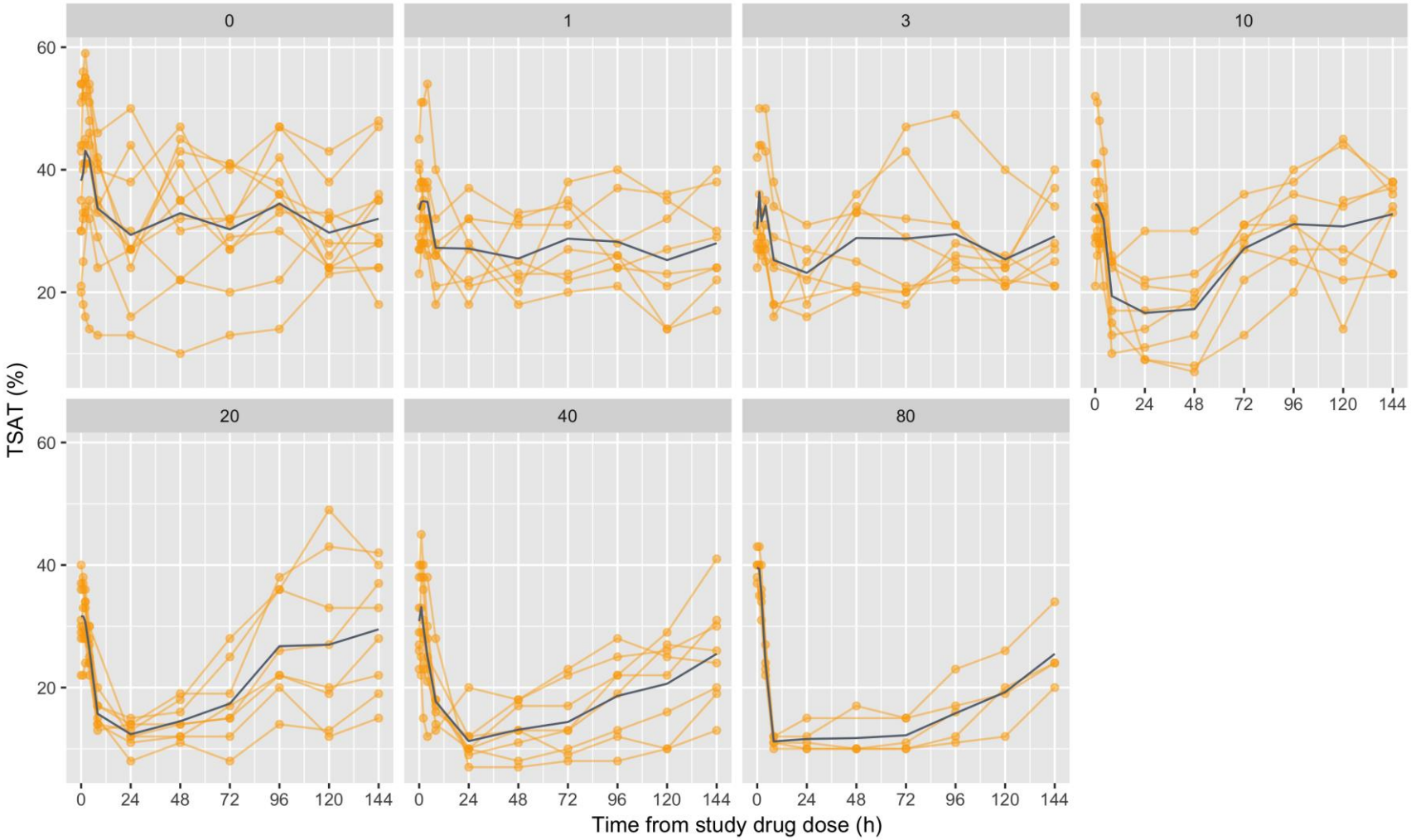


line shows FeAUC=a.1/PTG-300AUC+b (placebo subjects omitted from fit)

PTG-300 Induces a Dose-Dependent Reduction in TSAT

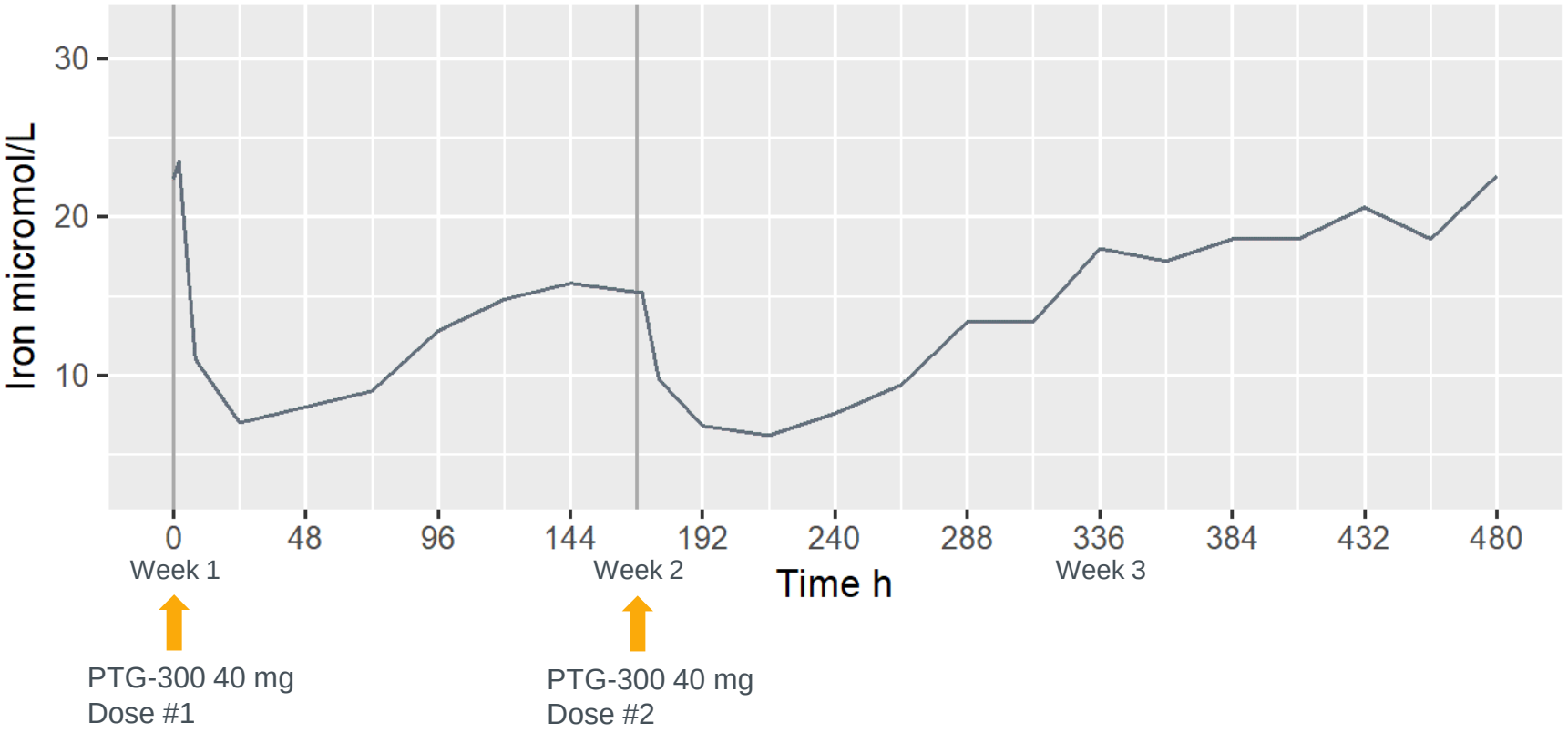
Similar effects on serum iron

Transferrin Saturation (TSAT)% by single dose level (individual subject and means)



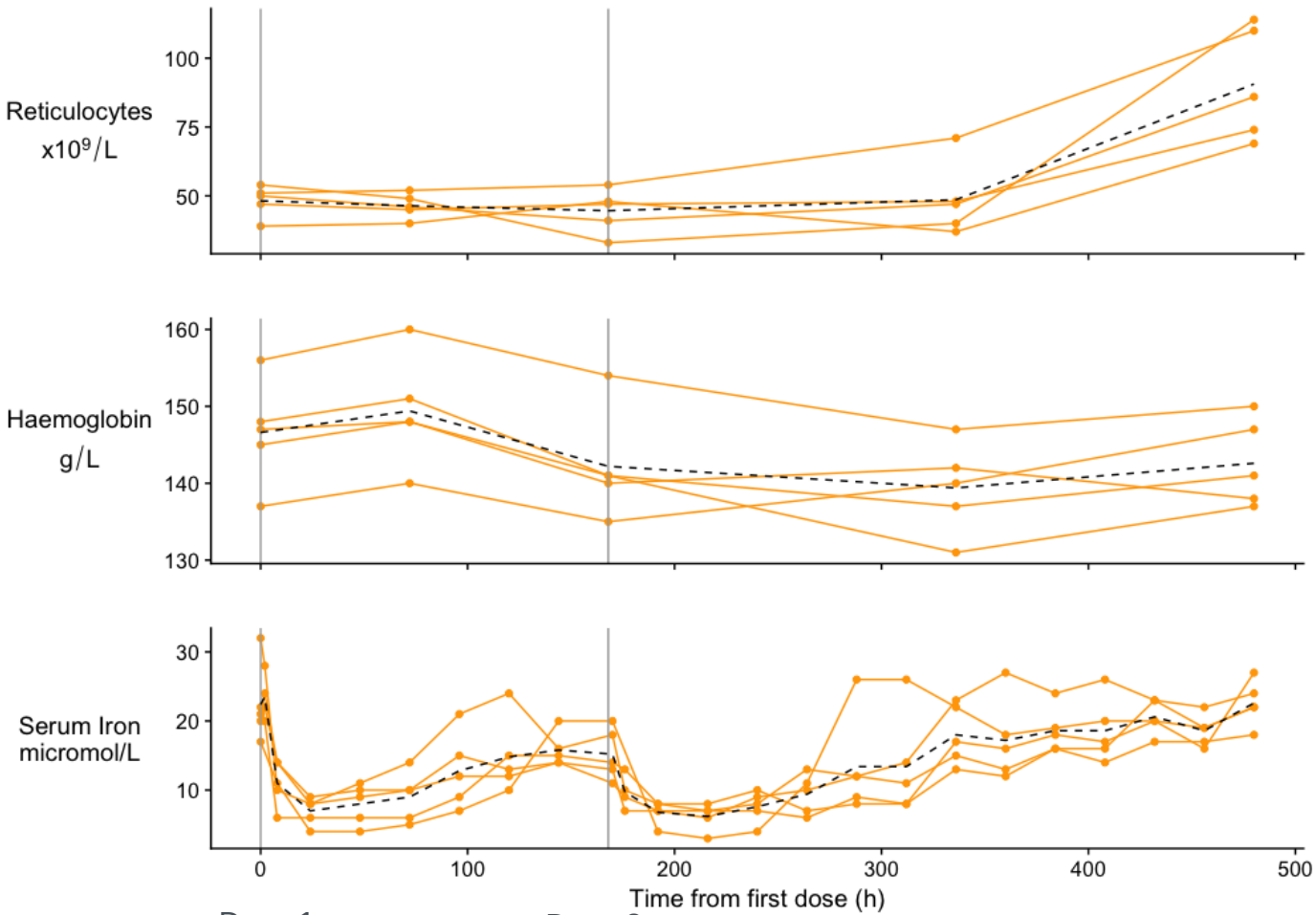
PTG-300 Effects on Serum Iron Comparable for both Doses

Recovery to Baseline 1-2 weeks after Second Dose

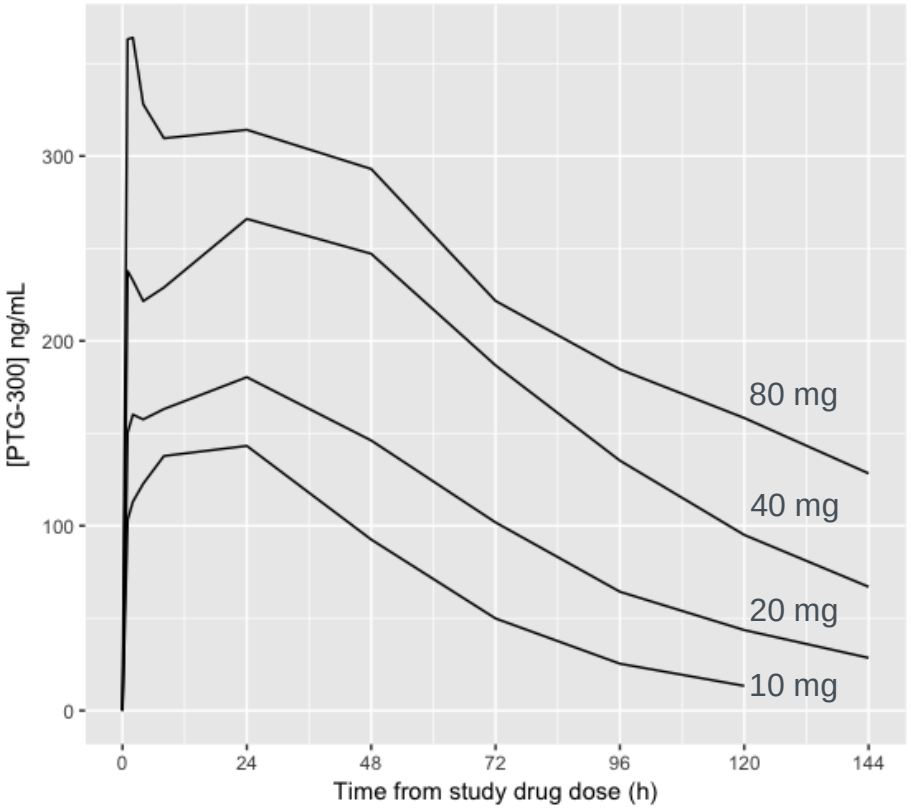


Post-Treatment Iron Recovery Associated with Reticulocytosis

Cohort 7 individual subjects and means (n=5)



PTG-300 PK Predictable and Well-Characterized



	Dose			
	10 mg n=8	20 mg n=7	40 mg n=8	80 mg n=5
AUC_{last} (ng.h/ml)	9071 (2230)	14860 (2668)	26580 (11529)	47100 (11496)
C_{max} (ng/ml)	148 (52)	189 (34)	317 (127)	415 (88)
T_{max} (h)	24	24	4.5	2
$t_{1/2}$ (h)	26 (7)	35 (10)	45 (12)	52 (17)

- Exposure increased somewhat less than proportionally with dose

PTG-300 Well-Tolerated Following Single Dose Exposure

Overall Summary of Treatment Emergent Adverse Events (single dose)

Adverse Event Summary	PTG-300 1 mg (N=8)	PTG-300 3 mg (N=8)	PTG-300 10 mg (N=8)	PTG-300 20 mg (N=8)	PTG-300 40 mg (N=8)	PTG-300 80 mg (N=5)	All PTG-300 (N=45)	All Placebo (N=11)
Subjects	4 (50.0%)	5 (62.5%)	7 (87.5%)	6 (75.0%)	5 (62.5%)	4 (80.0%)	31 (68.9%)	4 (36.4%)
Total Events	4	10	11	12	6	9	52	5
Total Unique Events	4	7	7	5	3	7	18	4
Subjects with Treatment-related AEs	1 (12.5%)	2 (25.0%)	6 (75.0%)	6 (75.0%)	4 (50.0%)	4 (80.0%)	23 (51.1%)	1 (9.1%)
SAEs	0	0	0	0	0	0	0	0
Injection site reactions	1 (12.5%)	1 (12.5%)	5 (62.5%)	6 (75.0%)	3 (37.5%)	3 (60.0%)	19 (42.2%)	1 (9.1%)
Headache	-	2 (25.0%)	2 (25.0%)	2 (25.0%)	1 (12.5%)	2 (40.0%)	9 (20.0%)	1 (9.1%)
Upper respiratory tract infection	1 (12.5%)	3 (37.5%)	-	1 (12.5%)	2 (25.0%)	1 (20.0%)	8 (17.8%)	1 (9.1%)

- Repeat dose cohort: 4/5 subjects with injection site reactions; single events: costochondritis, headache, acne
- No clinically significant changes in safety labs, VS, ECGs

PTG-300 Phase 1 Summary

- PTG-300 demonstrated marked and sustained dose-related effects on iron distribution in healthy volunteers
  - Consistent with activities of hepcidin and pre-clinical studies of PTG-300.
- Systemic exposure increased with dose; minimal drug accumulation observed following repeat dose administration
- PTG-300 was well-tolerated following single and repeat dose injection; A transient injection site erythema was observed in some subjects

PTG-300 Phase 1 Conclusions

- This Phase 1 study establishes PD-based proof-of-concept and provides a range of doses that can be evaluated in the treatment of diseases of ineffective erythropoiesis and iron overload.

- A global phase 2 study in patients with transfusion-dependent and non-transfusion-dependent β-thalassemia is currently planned.