Luspatercept Increases Hemoglobin, Reduces Liver Iron Concentration and Improves Quality of Life in Non-Transfusion Dependent Adults with Beta-Thalassemia

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Abstract P758

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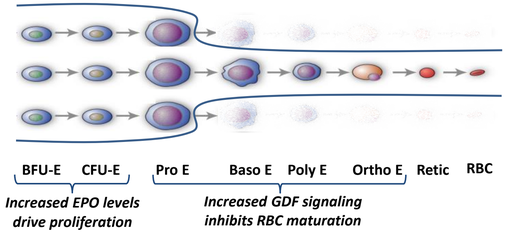
Introduction

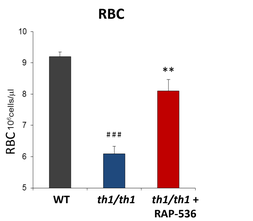
- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to ineffective erythropoiesis characterized by apoptosis of maturing erythroblasts in the bone marrow
- Excess GDF11 and other TGF-β superfamily ligands increase Smad 2/3 signaling and block RBC maturation, resulting in erythroid hyperplasia in the bone marrow

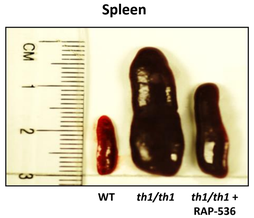


- **Luspatercept** is an investigational drug that is a recombinant fusion protein containing a modified extracellular domain (ECD) of the activin receptor type IIB (ActRIIB)
- Luspatercept binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythroid differentiation[1]
- Luspatercept increased hemoglobin levels in healthy volunteers[2] and patients with myelodysplastic syndromes[3]

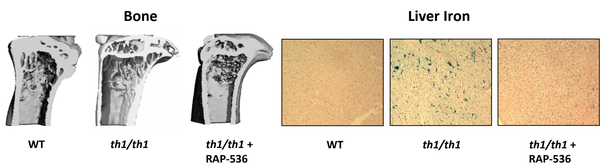
Non-Clinical Studies

- RAP-536 (murine luspatercept) reduces ineffective erythropoiesis and disease burden in mouse model of β-thalassemia[4,5]





p< 0.001 vs WT; ** p< 0.01, *p<0.05 vs *th1/th1*



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Methods

- This is an ongoing, Phase 2, multicenter, open-label study in adults with β-thalassemia (data as of 11Mar2016)
  - Non-transfusion dependent (NTD): < 4 units/8 wk, Hb <10 g/dL
  - Transfusion dependent (TD): ≥ 4 units/8 wk
- Primary efficacy endpoints (over 8 or 12 wk)
  - NTD: Hemoglobin increase ≥ 1.0 or ≥1.5 g/dL
  - TD: Transfusion burden decrease ≥ 20% or ≥ 50%
- Secondary endpoints include:
  - Safety, liver iron concentration (LIC, by MRI), health-related quality of life (FACT-An), biomarkers
- Data for TD patients are presented separately **(abstract S836)**

Study Design

- Dose levels (SC q3 weeks)
  - **Base study** dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, and 1.25 mg/kg and expansion cohort (n=29): starting dose 0.8 mg/kg, titration up to 1.25 mg/kg (total n=64)
  - **Extension study** (n=51): 0.8-1.25 mg/kg
- Follow-up
  - All patients are followed for 2 months post treatment completion or early discontinuation

Base Study (n=64)
3 Months
NCT01749540

→

Extension Study (n=51)
→ 2 years (ongoing)
NCT02268409

NTD: n=34
- n=12 lower dose levels (0.2-0.4)
- n=22 higher dose levels (≥ 0.6)

NTD: n=27
- higher dose levels

NTD Patients: Baseline Characteristics

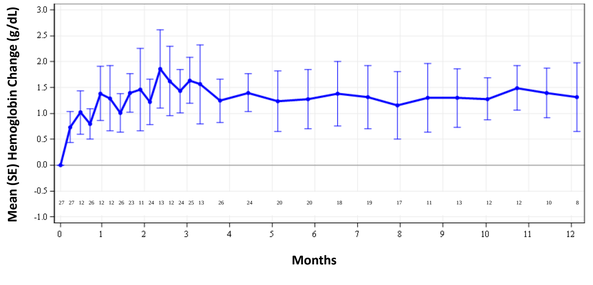
Parameter	Base Study N=34	Extension Study N=27
Age, yr, median (range)	38.5 (20-62)	37 (23-62)
Sex, male, n (%)	21 (62%)	17 (63%)
Splenectomy, n (%)	23 (68%)	18 (67%)
Hemoglobin, g/dL, median (range)	8.5 (6.5-9.8)	8.7 (7.6-9.8)
LIC, mg/g dry wt, mean ± SD	5.5 ± 3.8	4.9 ± 3.4

LIC: liver iron concentration (by MRI)

NTD Patients: Hemoglobin Change

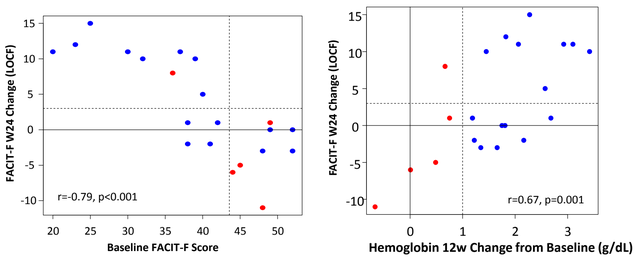
Hemoglobin response over a 12 wk period vs 12 wk pre-treatment	Patients Treated with ≥ 0.6 mg/kg with Hb Response, n (%)	
	Base Study N=22	Extension Study N=27
Increase in mean Hb ≥ 1.0 g/dL	14 (64%)	21 (78%)
Increase in mean Hb ≥ 1.5 g/dL	8 (36%)	15 (56%)

- Sustained increase in hemoglobin with long term treatment
- Median time to response was 8 days
- Duration of response (change in Hb ≥ 1.0 g/dL) ranged from 113 to 505+ days



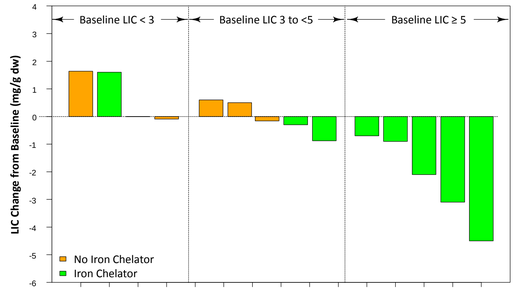
NTD Patients: Quality of Life Assessments

- FACIT-F is a 13-question patient-reported outcome (PRO) questionnaire (subscore of FACT-An) used to assess anemia related symptoms (e.g., fatigue)
- 9/13 (69%) patients with baseline deficit (<44) improved by ≥ 3 points (proposed minimal clinically important difference) at 24 wks (last observation carried forward)
- Increase in mean hemoglobin over a 12-wk period correlated with increase in FACIT-F (r=0.67, p=0.001)



NTD Patients: Liver Iron Concentration (MRI)

- 60% (3/5) of patients treated for ≥ 6 months with baseline LIC ≥ 5 had decrease in LIC ≥ 2 mg/g dw
- 89% (8/9) patients with baseline LIC < 5 maintained LIC < 5 mg/g dw



Safety Results

- No related serious adverse events in either study
- One grade 3 related adverse event of headache (n=1, extension)
- Reasons for discontinuation in NTD patients included non-compliance (n=2) and prohibited medication, headache, bone pain, lost to follow-up, and patient request (n=1 each)

Preferred Term	Patients with Related AEs (all grades) in > 10% NTD Patients, n (%)	
	NTD Patients N=34	Overall N=64
Bone pain	9 (27%)	24 (38%)
Headache	9 (27%)	16 (25%)
Musculoskeletal pain	6 (18%)	10 (16%)
Arthralgia	5 (15%)	13 (20%)

Summary/Conclusions

- Luspatercept was generally safe and well-tolerated
- Sustained hemoglobin increase was observed in the majority of NTD patients in the higher dose groups and correlated with an improvement in Quality of Life
- Reductions in liver iron concentration were also observed
- These results support further investigation of luspatercept in patients with non-transfusion dependent β-thalassemia
- A Phase 3 study of luspatercept in regularly transfused patients with β-thalassemia is currently enrolling patients (The BELIEVE Study; **NCT02604433**)

References

[1] Suragani R et al., Nature Med 2014
[2] Attie, K et al., Am J Hematol 2014
[3] Platzbecker U et al., EHA 2016 **abstract S131**
[4] Suragani R et al., Blood, 2014
[5] Martinez P et al., EHA 2016 **abstract S136**