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Long-term efficacy and safety outcomes in the phase 2 study of luspatercept in β-thalassemia

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Introduction

- β-thalassemia is a hereditary blood disorder caused by mutations in the β-globin gene that lead to impaired synthesis of β-globin, ineffective erythropoiesis, and anemia[1,2]
- Patients with β-thalassemia may require regular blood transfusions, as well as iron chelation therapy to minimize the toxic effects of iron accumulation[3]
- Anemia and the other complications of β-thalassemia have a significant effect on patients' lives, and there remains a significant unmet need to improve the health-related quality of life of patients with β-thalassemia[4,5]
- Luspatercept is a first-in-class erythroid maturation agent approved in the USA and Europe for the treatment of adult patients with transfusion-dependent (TD) β-thalassemia[6]
- Luspatercept binds to selected TGF-β superfamily ligands, reducing aberrant Smad2/3 signaling and promoting late-stage erythroid maturation[7]
- In a phase 2 study in patients with either TD or non-transfusion-dependent (NTD) β-thalassemia (NCT01749540), luspatercept increased hemoglobin (Hb) levels in NTD patients, reduced transfusion burden in TD patients, was well tolerated, and allowed the design of a 5-y extension study (NCT02268409)[8]

Objective

- The objective of this study was to evaluate long-term efficacy and safety in patients enrolled in the phase 2 3-month dose-escalation study followed by a 5-year extension (NCT01749540, NCT02268409) of luspatercept in β-thalassemia

Methods

Study design

- This single-arm, phase 2, open-label study evaluated the effects of luspatercept in patients with β-thalassemia
  - Patients received luspatercept for up to 3 mo in the base study (0.2-1.25 mg/kg SC q3w)
  - Patients were then eligible for treatment for up to 5 additional years in the extension study (0.8-1.25 mg/kg SC q3w)
- Eligible patients were:
  - ≥ 18 y of age
  - Receiving red blood cell (RBC) transfusions for ≥ 8 wk prior to enrollment
  - Considered NTD (< 4 RBC U/8 wk prior to first dose with baseline Hb < 10 g/dL), or TD (≥ 4 RBC U/8 wk prior to first dose, confirmed over 6 mo)

Study endpoints

- **Extension study primary endpoint:** long-term safety and tolerability of luspatercept in patients with β-thalassemia who were previously enrolled in the base study
- **Key secondary endpoints:**
  - Erythroid response:
    - NTD patients: mean Hb increase ≥ 1.5 g/dL over a continuous 8- or 12-wk interval compared with baseline
    - TD patients: reduction in RBC transfusion burden by ≥ 50% over a continuous 8- or 12-wk interval compared with the 12 wk prior to the start of treatment
  - Duration of erythroid response; mean change from baseline over an 8- or a 12-wk period in Hb level in NTD patients; mean % change from baseline in transfusion burden over 8 or 12 wk in TD patients
  - Iron overload; liver iron concentration (LIC) by MRI
- **Exploratory endpoints:** quality of life (FACIT-Fatigue); 6-min walk test (6MWT) distance in NTD patients

Results

Baseline characteristics

- As of June 18, 2020, 63 of the total enrollment of 64 patients were treated with dose levels of ≥ 0.6 mg/kg
- Of the 63 patients, 31 (49.2%) were NTD and 32 (50.8%) TD; median (range) age was 38 (20–62) y; 66.7% had prior splenectomy (**Table 1**)

Table 1. Baseline characteristics

Characteristic	Overall (N = 63)	TD (n = 32)	NTD (n = 31)
Age, median (range), y	38.0 (20–62)	38.5 (21–55)	38.0 (20–62)
Female, n (%)	30 (47.6)	19 (59.4)	11 (35.5)
Hb, median (range), g/dL	NA	NA	8.5 (6.5–9.8)
RBC transfusion burden, median (range), U/16 wk	NA	8.3 (4-18)	NA
LIC, n	62	31	31
Mean (SD), mg/g dw	5.0 (4.14)	4.7 (4.65)	5.3 (3.62)
Serum ferritin, mean (SD), µg/L	807.7 (614.55)	985.5 (737.66)	624.2 (386.98)
Prior iron chelation therapy, n (%)	46 (73.0)	30 (93.8)	16 (51.6)
Splenectomy, n (%)	42 (66.7)	21 (65.6)	21 (67.7)

dw, dry weight; NA, not assessed; SD, standard deviation.

Efficacy: NTD patients

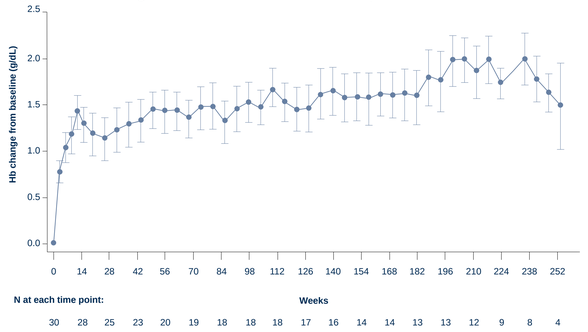
- The median (range) duration of treatment was 2.50 (0.11–5.07) y for NTD patients
- Of 31 NTD patients, 22 (71.0%) achieved a mean Hb increase ≥ 1.0 g/dL, and 17 (54.8%) achieved a mean Hb increase ≥ 1.5 g/dL over any 12 wk vs baseline
  - The mean (SD) Hb increase over any 12-wk period was 1.7 (1.07) g/dL
- The median (range) longest duration of Hb increase ≥ 1.0 g/dL was 3.47 (0.33–5.15) y and 2.57 (0.35–4.90) y for Hb increase ≥ 1.5 g/dL (**Table 2**)
- Mean Hb increase in NTD patients exceeded 1.0 g/dL by week 6 and was sustained throughout the extension study (**Figure 1**)
  - The mean (SD) maximum increase in Hb at any time was 2.1 (1.08) g/dL
- Improvement in FACIT-Fatigue score in NTD patients correlated with change in Hb level at week 24 (r = 0.71, *P* = 0.0015) (**Figure 2**)
- Improvement in 6MWT distance in NTD patients trended with change in Hb level at week 48 (n = 9, r = 0.64, *P* = 0.0658)
- Mean lactate dehydrogenase (LDH) decreased from wk 96 in NTD responders (**Figure 3**)

Table 2. Hb response in NTD patients

	Response rate, n/N (%) (95% CI)	Duration of longest response, median (range), y	Number of responses, median (range)	Cumulative duration of response, median (range), y
Hb increase over any 12-wks				
≥ 1.0 g/dL, n (%) (95% CI)	22/31 (71.0) (52.0–85.8)	3.47 (0.33–5.15)	1 (1-6)	3.47 (0.33–5.15)
≥ 1.5 g/dL, n (%) (95% CI)	17/31 (54.8) (36.0–72.7)	2.57 (0.35–4.90)	1 (1-9)	3.08 (0.35–4.90)
Mean Hb increase, n	29	NA	NA	NA
g/dL, mean (SD)	1.7 (1.07)			

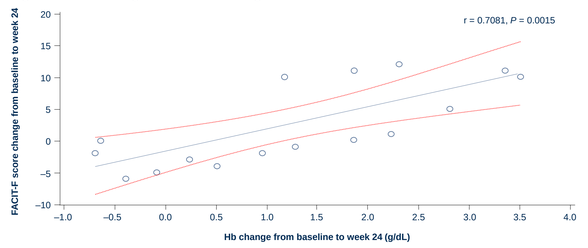
NA, not applicable.

Figure 1. Mean change in Hb level from baseline for NTD patients



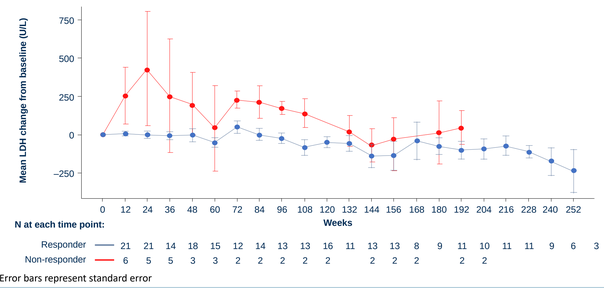
n = 30. Error bars represent standard error.

Figure 2. FACIT-Fatigue versus Hb change from baseline at week 24



Pearson correlation was used to evaluate the relationship between FACIT-Fatigue score change and Hb change from baseline.

Figure 3. Mean change in LDH from baseline for NTD patients by Hb response



Error bars represent standard error

Efficacy: TD patients

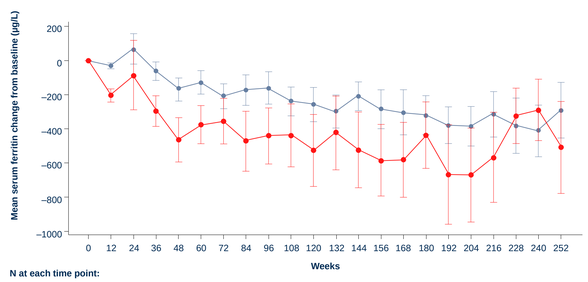
- The median (range) duration of treatment was 1.2 (0.06–4.90) y for TD patients
- Of the 32 TD patients, 22 (68.8%) achieved a ≥ 33% reduction in transfusion burden over any 12-wk interval vs baseline, including 19 (59.4%) TD patients that achieved a ≥ 50% reduction
  - The mean (SD) maximum change in transfusion burden was 65.4% (25.62%)
- The median (range) longest duration of ≥ 33% reduction in transfusion burden was 0.56 (0.25–4.75) and 0.40 (0.24–4.75) y for ≥ 50% reduction (**Table 3**)
- Nine of 32 (28.1%) patients who were TD at baseline achieved RBC transfusion independence, defined as any transfusion-independent interval of ≥ 8 wk
- There was a trend for decreased mean serum ferritin levels from baseline for NTD and TD patients treated in the extension study; this trend was maintained at week 252 (4.8 y after start) (**Figure 4**)

Table 3. RBC transfusion reduction in TD patients[a]

Response rates	Response rate, n/N (%) (95% CI)	Duration of longest response, median (range), y	Number of responses, median (range)	Cumulative duration of response, median (range), y
RBC transfusion reduction in any 12-wks				
≥ 33%, n (%) (95% CI)	22/32 (68.8) (50.0–83.9)	0.56 (0.25–4.75)	2.5 (1–42)	3.14 (0.25–4.79
≥ 50%, n (%) (95% CI)	19/32 (59.4) (40.6–76.3)	0.40 (0.24–4.75)	5.0 (1–42)	2.49 (0.24–4.75)
Maximum change in transfusion burden from baseline, n	23	NA	NA	NA
%, mean (SD)	65.4 (25.62)			

NA, not applicable.

Figure 4. Mean change in serum ferritin in NTD and TD patients

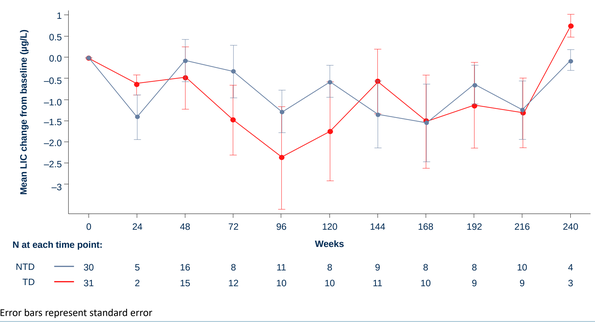


Error bars represent standard error.

Efficacy: LIC

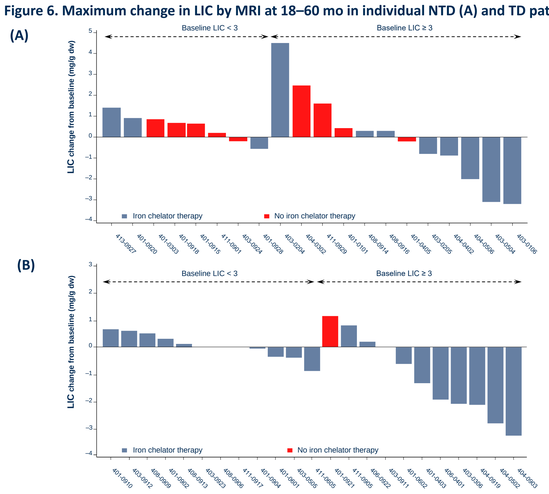
- Decreases in mean LIC were observed in NTD and TD patients during the course of the study (**Figure 5**)
- Greater decreases in LIC were observed in patients who had baseline LIC ≥ 3 mg/g dw and were on iron chelation therapy (**Figure 6**)

Figure 5. Mean change in LIC by MRI



Error bars represent standard error

Figure 6. Maximum change in LIC by MRI at 18–60 mo in individual NTD (A) and TD patients (B)



The average LIC value is used to calculate change from baseline for patients with multiple LIC records in one analysis window.

Safety

- 56 of 64 (87.5%) patients experienced a related treatment-emergent adverse event (TEAE) of any grade, including 8 (12.5%) patients who experienced a grade 3 or 4 TEAE (**Table 4**)
  - Four (6.3%) patients experienced a serious grade 3 or above TEAE related to study drug including 1 each of biliary colic, bone marrow failure, cerebrovascular accident, priapism, and tibia fracture

Table 4. Safety

Preferred term	Related TEAE, n (%)	
	Any grade (N = 64)	Grade 3 or 4 (N = 64)
Any related TEAE	56 (87.5)	8 (12.5)
Bone pain	27 (42.2)	3 (4.7)
Headache	20 (31.3)	1 (1.6)
Myalgia	14 (21.9)	0
Arthralgia	12 (18.8)	1 (1.6)
Musculoskeletal pain	11 (17.2)	0
Asthenia	9 (14.1)	2 (3.1)
Injection site pain	9 (14.1)	0
Back pain	6 (9.4)	0
Extramedullary hemopoiesis	4 (6.3)	0

Conclusions

- In this assessment of longer-term outcomes in patients with β-thalassemia, luspatercept treatment was associated with sustained increases in Hb levels in NTD patients, and sustained decreases in transfusion burden in TD patients
- There was a trend for a decrease in mean serum ferritin levels in NTD and TD patients
- Decreases in LIC were observed in all patients, particularly those who had higher baseline LIC and were on iron chelation therapy
- Luspatercept was associated with a tolerable safety profile over the extended observation period

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References

1. Weatherall DJ. *Nat Rev Genet* 2001;2:245–255.
2. Musallam KM, et al. *Haematologica* 2013;98:833–844.
3. Poggiali E, et al. *Blood Transfus* 2012;10:411–422.
4. Sobota A, et al. *Am J Hematol* 2011;86:92–95.
5. Amid A, et al. *Blood* 2016;128(22). Abstract 3633.
6. US Food and Drug Administration (FDA). FDA news release. FDA website, https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-treat-patients-rare-blood-disorder. Published November 8, 2019. Accessed April 28, 2021.
7. Attie K, et al. *Am J Hematol* 2014;89:766–770.
8. Piga A, et al. *Blood* 2019;133:1279–1289.

Disclosures

Piga: *BMS*: research funding, personal fees, non-financial support, and advisory boards. **Tartaglione:** *BMS*: advisory board; *bluebird bio*: consultancy. **Voskaridou:** *Celgene*: consultancy, research funding; *BMS*: consultancy, research funding; *Protagonist Therapeutics*: research funding; *Genesis Therapeutics Inc.*: consultancy, research funding; *Novartis International AG*: research funding; *addmedica*: consultancy, research funding; *Imara Inc.*: research funding. **Zhang:** *Acceleron*: employment. **Shetty:** *BMS*: employment. **Attie:** *Acceleron*: stocks. **Pietrangelo, Ricchi, Gamberini, Caruso:** nothing to disclose.

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