A phase 2 study of luspatercept in adults and adolescents with α-thalassemia: findings from the dose-confirmation cohort in adolescents

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Introduction

- α-thalassemia hemoglobin H (HbH) disease results from impaired Hb synthesis, associated ineffective erythropoiesis and peripheral hemolysis, generally manifesting as anemia, as well as other complications such as thromboembolic events, extramedullary hematopoiesis (EMH), and iron overload[1]
- Currently, management is largely supportive, including transfusions and iron chelation therapy (ICT) when needed
  - As a result, patients can face long-term issues related to chronic anemia and reduced quality of life[1]
- Luspatercept is approved for treating anemia in adults with β-thalassemia with the following indications:
  - China: patients who require red blood cell (RBC) transfusions (≤ 15 RBC units/24 weeks)[2]
  - EU: patients with transfusion-dependent (TD) and non-transfusion-dependent (NTD) disease[3]
  - Taiwan: patients with NTD disease with Hb < 10 g/dL at treatment initiation[4]
  - USA: patients who require regular RBC transfusions[5]
- The efficacy and safety of luspatercept versus placebo for the treatment of anemia in adult patients with α-thalassemia are being evaluated in a phase 2, multicenter study (NCT05664737)[6]
  - As part of the study, the safety and tolerability of luspatercept are being assessed in adolescents with TD or NTD α-thalassemia HbH disease in an open-label arm

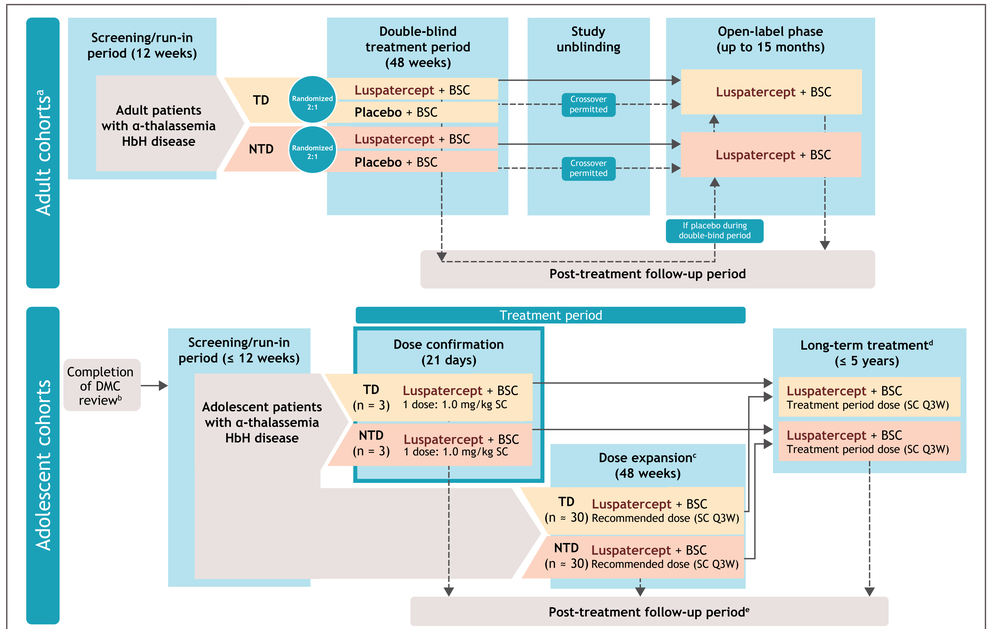
Objective

- To report safety data from 6 patients with TD or NTD α-thalassemia HbH disease who received luspatercept in the dose-confirmation phase of the adolescent cohort

Methods

- In this phase 2, multicenter study, luspatercept is being evaluated for the treatment of anemia in patients with TD or NTD α-thalassemia HbH disease (**Figure 1**)
  - The efficacy and safety of luspatercept versus placebo are being evaluated in the randomized, double-blind, placebo-controlled adult cohort
  - In the open-label, adolescent cohort arm, luspatercept safety and pharmacokinetics are being evaluated
- Key eligibility criteria for the adolescent cohorts are shown in **Figure 2**
- Adolescent patients were enrolled in TD and NTD dose-confirmation cohorts (n = 3 each) in which they received a single 21-day cycle of treatment consisting of 1 dose of luspatercept at the recommended dose of 1.0 mg/kg SC and were evaluated for safety and tolerability
  - The recommended dose was determined based on results of luspatercept in adolescent patients with β-thalassemia (ACE-536-B-THAL-004; NCT04143724)[7]
- Upon completion of dose confirmation, the dose-expansion phase began enrolling (n = 30 each planned for separate TD and NTD cohorts), in which patients receive luspatercept at the recommended dose every 21 days for 48 weeks
- Following completion of the dose-confirmation or dose-expansion phases, patients can enter a long-term treatment phase (lasting up to 5 years from the first dose) and a post-treatment follow-up period (5 years from the first dose or 3 years after the last dose, whichever occurs later)
- The data cutoff date for this analysis was March 3, 2025

Figure 1. Overall study design



[a]The full study design for the adult cohorts has been reported previously[6]; [b]Enrollment in the adolescent cohorts may begin only after initial DMC review of n = 15 patients from the adult cohort treated for ~ 3 months determines that adult enrollment may continue; [c]Enrollment in the dose-expansion phase to be initiated after evaluation of the dose-confirmation cohorts for DLTs; luspatercept to be given at the recommended dose from the dose-confirmation cohort; [d]Patients can continue to receive luspatercept at the same dose as during the treatment period for up to 5 years from their first dose; [e]Patients discontinuing treatment at any time will continue to be followed for 5 years from their first dose or 3 years post last dose, whichever occurs later. BSC, best supportive care; DLT, dose-limiting toxicity; DMC, Data Monitoring Committee; Q3W, every 3 weeks; SC, subcutaneously.

Figure 2. Key eligibility criteria for adolescent cohorts

Inclusion criteria	Exclusion criteria
• 12 to < 18 years of age • Diagnosis of α-thalassemia HbH disease • TD, defined as: - ≥ 4 RBC events[a] during the 24 weeks prior to enrollment - No transfusion-free period > 56 days during the 24 weeks prior to enrollment - History of regular transfusions for ≥ 2 years • NTD, defined as: - < 4 RBC events[a] during the 24 weeks prior to enrollment - RBC transfusion-free during ≥ 8 weeks prior to enrollment - Baseline Hb ≤ 10 g/dL based on 2 measurements ≥ 1 week apart within 4 weeks prior to enrollment • Karnofsky PS (≥ 16 years of age) or Lansky PS (< 16 years of age) scores ≥ 50 at screening	• Diagnosis of α-thalassemia trait, Hb Bart hydrops, ATRx, HbS/β-thalassemia, myelodysplasia subtype anemia, or HbE homozygous β gene mutation • Anemia or hemolysis not related to α-thalassemia • Patients with DVT, stroke or other thromboembolic event(s) during the 24 weeks prior to enrollment • Previous or concomitant HSCT or gene therapy • Use of ESA or hydroxyurea treatment ≤ 12 weeks (NTD) or ≤ 24 weeks (TD) prior to enrollment • ICT initiated during the 24 weeks prior to enrollment • Patients who had EMH complications requiring treatment

[a]An RBC event is defined as a single occurrence of an RBC transfusion (transfusions administered over 2 or 3 consecutive days are considered a single transfusion event).
ATRx, α-thalassemia mental retardation syndrome; DVT, deep-vein thrombosis; ESA, erythropoiesis-stimulating agent; Hb Bart hydrops, Hb Bart's hydrops fetalis; HSCT, hematopoietic stem cell transplant; PS, performance status.

Results

Patient demographics and disease characteristics

- Overall, 3 adolescent patients with α-thalassemia HbH disease were enrolled in each of the TD and NTD dose-confirmation cohorts
- Baseline patient demographics for the TD and NTD cohorts are shown in **Table 1**
  - In the TD cohort all patients were male, and in the NTD cohort all were female
  - All patients were Asian in both cohorts
- Baseline disease characteristics for the TD and NTD cohorts are shown in **Table 2**
  - All patients in the TD cohort had a baseline Hb level ≥ 8.5 g/dL, while in the NTD cohort, 2 of the 3 patients (66.7%) had a baseline Hb level < 8.5 g/dL
  - The median (range) baseline transfusion burden was 6.0 RBC units/24 weeks (4.0-6.0) in the TD cohort; in the NTD cohort, 1 patient had received a transfusion at baseline (2.0 RBC units)
  - In the TD cohort, all patients had Karnofsky PS or Lansky PS scores of 100, while scores were ≥ 70 in the NTD cohort
  - All patients in the TD cohort and none in the NTD cohort received prior ICT (all deferasirox)
  - All patients had ≥ 1 comorbidity at baseline

Table 1. Baseline demographics

Demographic	TD cohort (n = 3)	NTD cohort (n = 3)
Age, median (range), years	14 (13.0-17.0)	17 (16.0-17.0)
Sex, n (%)		
Male	3 (100)	0
Female	0	3 (100)
Race, n (%)		
Asian	3 (100)	3 (100)
Country, n (%)		
China	2 (66.7)	1 (33.3)
Taiwan	1 (33.3)	2 (66.7)

Table 2. Baseline disease characteristics

Characteristic	TD cohort (n = 3)	NTD cohort (n = 3)
Hb level, n (%)		
< 8.5 g/dL	0	2 (66.7)
≥ 8.5 g/dL	3 (100)	1 (33.3)
Transfusion burden, median (range), RBC units/24 weeks	6.0 (4.0-6.0)	n = 1 2.0
Karnofsky/Lansky PS score, n (%)[a]		
70	0	1 (33.3)
100	3 (100)	2 (66.7)
Splenectomy, n (%)		
Yes	1 (33.3)	0
No	2 (66.7)	3 (100)
Serum ferritin, median (range), µg/L	785.5 (426.5-1535.5)	106 (23.5-584.0)
LIC by MRI, median (range), mg/g dw	8.2 (4.3-27.0)	1.7 (1.6-3.5)
MRI myocardial T2*, median (range), ms	34.5 (25.7-34.6)	46.2 (45.2-46.8)
BMD DEXA scan for total hip, median (range), g/cm²	0.7 (0.7-0.8)	n = 2[b] 0.9 (0.8-0.9)
BMD DEXA scan for lumbar spine, median (range), g/cm²	0.6 (0.6-0.7)	0.9 (0.8-0.9)
Hip T or Z score, n (%)		n = 2[b]
> −1	0	1 (50.0)
> −2.5 to ≤ −1	1 (33.3)	1 (50.0)
≤ −2.5	2 (66.7)	0
Lumbar spine T or Z score, n (%)		
> −2.5 to ≤ −1	0	2 (66.7)
≤ −2.5	3 (100)	1 (33.3)
Prior ICT, n (%)	3 (100)	0
Deferasirox	3 (100)	0
Patients with ≥ 1 comorbidity, n (%)	3 (100)	3 (100)
Splenomegaly[c]	2 (66.7)	2 (66.7)
Clinically significant iron overload (NTD)[d]	-	0
Clinically significant iron overload (TD)[e]	2 (66.7)	-
Jaundice	1 (33.3)	0
Low bone mineral mass or BMD[f] by DEXA	2 (66.7)	2 (66.7)
Cholelithiasis	1 (33.3)	1 (33.3)
Splenectomy	1 (33.3)	0
Cholecystitis	0	1 (33.3)
Bone pain	1 (33.3)	0
Hypothyroidism	0	1 (33.3)

[a]Karnofsky PS score if ≥ 16 years of age or Lansky PS score if < 16 years of age; [b]Data unavailable for 1 patient; [c]Based on physical exam, MRI, or ultrasound; [d]> 800 µg/L serum ferritin or LIC > 5 mg/g dw; [e]> 1000 µg/serum ferritin or LIC > 7 mg/g dw; [f]Defined as bone mineral content or areal BMD Z scores ≤ −2.0. BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; dw, dry weight; LIC, liver iron concentration; MRI, magnetic resonance imaging.

Safety

- Adverse events (AEs) reported during the dose-confirmation period (within 21 days from the first dose of study therapy) are shown in **Table 3**
  - TEAEs were reported in 2 of the 6 patients: one grade 1 dizziness and one grade 2 upper respiratory infection (both in the TD cohort)
  - No serious TEAEs or AEs of special interest (thromboembolic events, malignancies or pre-malignancies, extramedullary masses, or bone fractures) were reported in either cohort
- In either cohort, there were no dose-limiting toxicities (DLTs), defined as grade ≥ 3 hemolytic crises or other grade ≥ 3 AEs outside the expected safety profile occurring within 21 days of the first dose

Table 3. Summary of TEAEs for the dose-confirmation period

Patients, n (%)	TD cohort (n = 3)	NTD cohort (n = 3)
≥ 1 TEAE	2 (66.7)	0
≥ 1 grade 3/4 TEAE	0	0
≥ 1 serious TEAE	0	0
≥ 1 AE of special interest[a]	0	0

[a]Defined as thromboembolic events, malignancies or pre-malignancies, EMH masses, or bone fractures.
TEAE, treatment-emergent AE.

Conclusions

- In this analysis from the dose-confirmation phase of luspatercept in adolescent patients with TD or NTD α-thalassemia HbH disease, no DLTs or new safety signals were reported, suggesting that the recommended dose of 1.0 mg/kg is well tolerated in these patients
- These results support continuation of the dose-expansion phase of the study for both cohorts, with enrollment currently ongoing

References

1. Lal A, et al. *Am J Hematol* 2024;99:2164-2177.
2. REBLOZYL® (luspatercept for injection) [package insert]. Princeton, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; May 2024.
3. REBLOZYL® (luspatercept-aamt) [summary of product characteristics]. Utrecht, Netherlands: Celgene Distribution B.V.; April 2025.
4. REBLOZYL® (luspatercept for injection) [package insert]. Taipei, Taiwan: Bristol Myers Squibb Taiwan Ltd; March 2025.
5. REBLOZYL® (luspatercept-aamt) [package insert]. Summit, NJ: Celgene Corporation; April 2020.
6. Viprakasit V, et al. *HemaSphere* 2023;7(suppl 3). Abstract PB2535.
7. Kattamis A, et al. *HemaSphere* 2024;8(suppl 1). Abstract P1516.

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