Safety data from the non-transfusion-dependent dose-confirmation cohort: a phase 2a study of luspatercept in pediatric patients with ß-thalassemia

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Introduction

- In pediatric patients with non-transfusion-dependent (NTD) ß-thalassemia, underlying ineffective erythropoiesis resulting in chronic anemia, bone marrow expansion, and iron overload can lead to fatigue, impaired growth and development, and progressive organ complications[1]
- Improving anemia is critical to lowering the likelihood of long-term morbidities and irreversible complications later in life; however, effective treatments to maintain hemoglobin (Hb) levels in these patients are lacking[1]
  - Red blood cell (RBC) transfusions are typically only received in special circumstances, such as to support normal growth and development or in the case of infections[1,2]
- In adult patients with ß-thalassemia, luspatercept treatment results in a durable increase in Hb levels for patients who are NTD, and durable reduction in transfusion burden for patients who are transfusion-dependent (TD)[3,4]
- In a phase 2a study evaluating the safety and pharmacokinetics of luspatercept in pediatric patients with ß-thalassemia (NCT04143724; EudraCT 2022-502499-22-00), no dose-limiting toxicities (DLTs) or treatment-emergent adverse events (TEAEs) resulting in treatment discontinuation were reported in the dose-escalation cohort of patients who were TD[5]

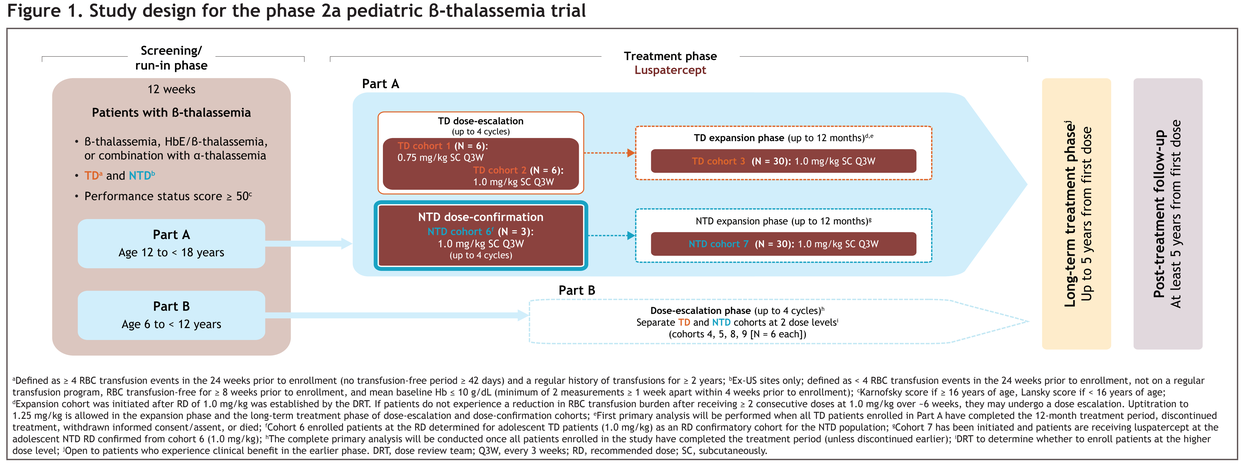
Objective

- To report safety data from adolescent patients in the NTD dose-confirmation cohort of the phase 2a study of luspatercept in pediatric ß-thalassemia

Methods

- This ongoing phase 2a study has a staggered design conducted in 2 parts, each with separate NTD and TD cohorts (**Figure 1**):
  - Part A: patients 12 to < 18 years of age
  - Part B: patients 6 to < 12 years of age
- This analysis focused on the NTD dose-confirmation cohort of part A (cohort 6)
- The treatment of NTD pediatric patients is being evaluated at sites outside of the USA; study locations include China, Germany, Greece, India, Italy, Thailand, and Türkiye

Figure 1. Study design for the phase 2a pediatric ß-thalassemia trial



[a]Defined as ≥ 4 RBC transfusion events in the 24 weeks prior to enrollment (no transfusion-free period ≥ 42 days) and a regular history of transfusions for ≥ 2 years; [b]Ex-US sites only; defined as < 4 RBC transfusion events in the 24 weeks prior to enrollment, not on a regular transfusion program, RBC transfusion-free for ≥ 8 weeks prior to enrollment, and mean baseline Hb ≤ 10 g/dL (minimum of 2 measurements ≥ 1 week apart within 4 weeks prior to enrollment); [c]Karnofsky score if ≥ 16 years of age, Lansky score if < 16 years of age; [d]Expansion cohort was initiated after RD of 1.0 mg/kg was established by the DRT. If patients do not experience a reduction in RBC transfusion burden after receiving ≥ 2 consecutive doses at 1.0 mg/kg over ~6 weeks, they may undergo a dose escalation. Uptitration to 1.25 mg/kg is allowed in the expansion phase and the long-term treatment phase of dose-escalation and dose-confirmation cohorts; [e]First primary analysis will be performed when all TD patients enrolled in Part A have completed the 12-month treatment period, discontinued treatment, withdrawn informed consent/assent, or died; [f]Cohort 6 enrolled patients at the RD determined for adolescent TD patients (1.0 mg/kg) as an RD confirmatory cohort for the NTD population; [g]Cohort 7 has been initiated and patients are receiving luspatercept at the adolescent NTD RD confirmed from cohort 6 (1.0 mg/kg); [h]The complete primary analysis will be conducted once all patients enrolled in the study have completed the treatment period (unless discontinued earlier); [i]DRT to determine whether to enroll patients at the higher dose level; [j]Open to patients who experience clinical benefit in the earlier phase. DRT, dose review team; Q3W, every 3 weeks; RD, recommended dose; SC, subcutaneously.

- NTD was defined as:
  - Receiving < 4 RBC transfusion events in the 24 weeks before enrollment (transfusions administered over 2 or 3 consecutive days are considered a single transfusion event)
  - Not being on a regular transfusion program
  - Being RBC transfusion-free for ≥ 8 weeks before enrollment
  - Having a mean baseline Hb level ≤ 10 g/dL
- Patients received luspatercept at 1.0 mg/kg SC Q3W for 4 cycles to confirm that the dose was well tolerated in adolescent patients with NTD ß-thalassemia
  - 1.0 mg/kg was previously identified as the RD based on the results of the adolescent TD cohorts[5]
- The data cutoff for this analysis was June 9, 2025

Results

Baseline demographics and disease characteristics

- The NTD dose-confirmation cohort (cohort 6) included 3 patients, 1 each from China, Italy, and Thailand
- Patients had a median age of 13.0 years (range, 12-17); 1 (33.3%) patient was female and 2 (66.7%) were male; and 1 (33.3%) patient was White and 2 (66.7%) were Asian (**Table 1**)
  - Two (66.7%) patients had ß-thalassemia and 1 (33.3%) patient had HbE/ß-thalassemia combined with α-thalassemia
  - No patient had a prior splenectomy or was receiving iron chelation therapy at baseline
  - One patient had comorbidities of splenomegaly and osteopenia, and 1 patient had splenomegaly, iron overload, and growth retardation

Treatment exposure

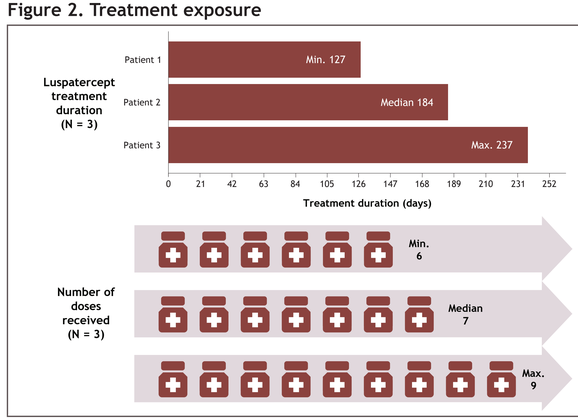
- The treatment duration and number of luspatercept doses received are shown in **Figure 2**
- A dose titration from 1.0 mg/kg to 1.25 mg/kg was experienced by 1 patient at day 65
- A dose delay was experienced by 1 patient at day 84 due to a Hb level ≥ 11.5 g/dL

Table 1. Baseline demographics and disease characteristics

Characteristic	Cohort 6 (N = 3)
Age, median (range), years	13.0 (12-17)
Female, n (%)	1 (33.3)
Race, n (%)	
Asian	2 (66.7)
White	1 (33.3)
Mutational status, n (%)	
ß-thalassemia	2 (66.7)
HbE/ß-thalassemia combined with α-thalassemia	1 (33.3)
Hb level, median (range), g/dL	7.8 (6.7-8.6)
LIC category by MRI, n (%)	
< 3 mg/g dw	2 (66.7)
> 7 to ≤ 15 mg/g dw	1 (33.3)
Splenectomy, n (%)	
No	3 (100)
Iron chelation therapy, n (%)	
No	3 (100)
Performance status score[a]	
Karnofsky (n = 1)	100
Lansky (n = 2)	90, 100
Patients with ≥ 1 comorbidity, n (%)	2 (66.7)
Splenomegaly	2 (66.7)
Iron overload	1 (33.3)
Osteopenia	1 (33.3)
Growth retardation	1 (33.3)

[a]Karnofsky performance status score if ≥ 16 years of age or Lansky performance status score if < 16 years of age.
dw, dry weight; LIC, liver iron concentration; MRI, magnetic resonance imaging.

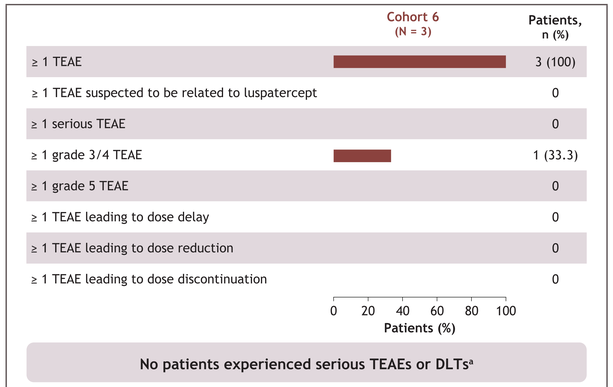
Figure 2. Treatment exposure



Safety

- All 3 patients experienced ≥ 1 TEAE (**Figure 3**, **Table 2**)
  - The reported grade 3/4 TEAE was a case of gastroenteritis
- There were no reports of serious TEAEs, grade 5 TEAEs, TEAEs leading to dose delay, or TEAEs suspected of being related to luspatercept treatment (**Figure 3**)

Figure 3. Summary of TEAEs



[a]DLTs were defined as any of the following occurring during cycle 1: treatment-related serious or treatment-related nonhematologic adverse event of grade ≥ 3, or treatment-related hematologic adverse event of grade ≥ 4.

Table 2. TEAEs

	Cohort 6 (N = 3)
TEAEs, n (%)[a]	
Upper respiratory tract infection	1 (33.3)
Gastroenteritis	1 (33.3)[b]
Abdominal pain	1 (33.3)
Toothache	1 (33.3)
Oropharyngeal pain	1 (33.3)
Influenza-like illness	1 (33.3)
Hyperuricemia	1 (33.3)
Headache	1 (33.3)

[a]Each patient could report more than 1 TEAE; [b]Grade 3/4.

Conclusions

- In this analysis of pediatric patients with NTD ß-thalassemia who received luspatercept at the starting dose of 1.0 mg/kg, safety data were consistent with results from the pediatric TD cohort at the same dose
  - There were no new safety signals, no patients experiencing serious TEAEs or DLTs, and no TEAEs suspected to be related to luspatercept treatment
  - TEAEs were generally nonhematologic in nature
- Based on the outcomes of the dose-confirmation phase, the study has proceeded to the dose-expansion phase in the NTD cohort, and patient recruitment is ongoing

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