# Evaluating luspatercept responders in the phase 3, randomised, double-blind, placebo-controlled BELIEVE trial of luspatercept in adult ß-thalassaemia patients who require regular red blood cell transfusions

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## Introduction

- ß-thalassaemia is a genetic blood disorder associated with ineffective erythropoiesis and anaemia[1]
- Patients with ß-thalassaemia who are transfusion dependent require frequent and lifelong red blood cell (RBC) transfusions and iron chelation therapy[2]
- Luspatercept is a first-in-class erythroid maturation agent that binds select TGF-ß superfamily ligands to diminish Smad2/3 signalling and enhance late-stage erythropoiesis[3,4]
  - In a phase 2 study, 23 (72%) transfusion-dependent patients receiving luspatercept achieved ≥ 33% reduction in RBC transfusion burden over a 12-week period[5]
  - The phase 3 BELIEVE trial met both primary (≥ 33% reduction in RBC transfusion burden with a reduction of ≥ 2 units, from Weeks 13–24 versus 12 weeks prior to randomisation) and secondary endpoints (≥ 33% reduction from baseline in RBC transfusion burden during Weeks 37–48 and ≥ 50% reduction during Weeks 13–24 and Weeks 37–48)[6]
  - Luspatacept has been approved by the EMA and US FDA for the treatment of adult patients with transfusion-dependent anaemia associated with ß-thalassemia

## Objective

- To evaluate the number of response episodes, duration of clinical benefit, and safety in luspatercept responders during the phase 3 BELIEVE study

## Methods

### Study design

- The BELIEVE study is an ongoing phase 3, double-blind, randomised, placebo-controlled, multicentre trial
  - The study was approved by the ethics committee and informed consent was obtained from all participants
- Adult patients with ß-thalassaemia or haemoglobin E/ß-thalassaemia (compound ß-thalassaemia mutation and/or multiplication of α-globin genes was allowed) requiring regular transfusions (6–20 RBC units in the 24 weeks prior to randomisation with no transfusion-free period > 35 days) were eligible for this study
- Patients were enrolled between July 2016 and June 2017 at 65 sites in 15 countries
- Patients were randomised 2:1 to luspatercept 1.0 mg/kg (titration up to 1.25 mg/kg allowed) or placebo, administered subcutaneously every 21 days for ≥ 48 weeks; additionally, all patients continued to receive best supportive care (**Figure 1**)
- The primary endpoint was achievement of RBC transfusion burden reduction ≥ 33%, with a reduction of ≥ 2 units in Weeks 13–24 versus the 12 weeks prior to randomisation
- After study unblinding, patients randomised to receive placebo were eligible to cross over and be treated with luspatercept

### Ad hoc analyses

- The data cutoff used for this analysis was January 7, 2019
- As part of these analyses, the following were assessed:
  - Achievement of response and number of response episodes
    - Achievement of response was defined as ≥ 33% reduction in RBC transfusion burden from baseline over any consecutive 24 weeks
  - Duration of clinical benefit
    - Clinical benefit was defined as the time from first response (≥ 33% reduction in RBC transfusion burden over any 24-week interval) to discontinuation due to any cause
  - Reduction in RBC units transfused during the study
  - Safety profile
  - Response assessment data for placebo patients are presented for the initial treatment period before crossover; data for the luspatercept arm includes only patients who were initially randomised to luspatercept

## Results

### Patients

- 336 patients were randomised as part of the BELIEVE trial; 223 of 224 received luspatercept and 109 of 112 received placebo (**Table 1**)
- After study unblinding, 92 of 109 (84.4%) patients in the placebo arm crossed over to the luspatercept arm
- Median treatment duration was 95.7 weeks (range 1.7–128.1) in the luspatercept arm and 74.7 weeks (range 8.9–104.0) in the placebo arm

### Response assessment

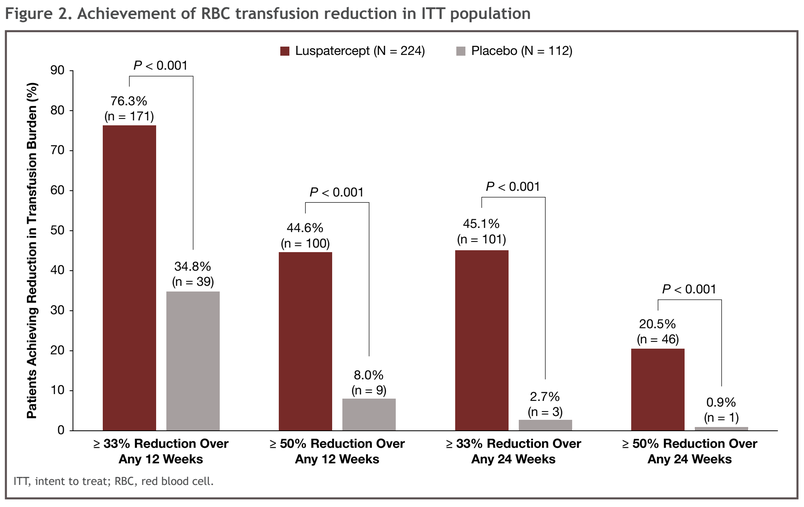
- 48 of 224 (21.4%) patients in the luspatercept arm and 5 of 112 (4.5%) patients in the placebo arm achieved the primary endpoint (≥ 33% reduction from baseline in RBC transfusion burden during Weeks 13–24 with a reduction of ≥ 2 units)[6]
- Treatment with luspatercept maintained pre-transfusion haemoglobin levels while reducing transfusion burden
  - The mean change in haemoglobin from pre-transfusion levels to post-baseline was from 0.09 to 0.38 g/dL for luspatercept-treated patients and from −0.04 to 0.10 g/dL for placebo-treated patients
- 101 of 224 (45.1%) of luspatercept-treated patients and 3 of 112 (2.7%) of placebo-treated patients achieved ≥ 33% reduction in RBC transfusion burden over any 24-week period (**Figure 2**)
- Of the 101 luspatercept responders, 74 experienced ≥ 2 separate response periods during any 24-week interval (**Table 2**)
  - Overall, 11 (4.9%) patients in the luspatercept arm experienced multiple episodes of response (defined as having ≥ 1 non-overlapping durations of response) during any 24-week interval
- Multiple response periods in patients achieving ≥ 33% reduction in transfusion burden over any 24-week interval are shown in **Figure 3**

**Table 1. Baseline characteristics of the BELIEVE ITT population**

| Characteristic[a] | Luspatercept (N = 224) | Placebo (N = 112) |
|---|---|---|
| Age, median (range), years | 30 (18-66) | 30 (18-59) |
| Female, n (%) | 132 (58.9) | 63 (56.3) |
| $B^0/B^0$, n (%) | 68 (30.4) | 35 (31.3) |
| Hb (24 week),[b] median (range), g/dL | 9.31 (4.5-11.4) | 9.15 (5.8-11.7) |
| RBC transfusion burden, median (range), units/12 weeks | 6.1 (3-14) | 6.3 (3-12) |
| RBC transfusion burden, median (range), units/24 weeks | 14 (6-24) | 15 (6-26) |
| Splenectomy, n (%) | 129 (57.6) | 65 (58.0) |
| Serum ferritin, mean (SD), µg/L | 2,097 (1,757) | 1,845 (1,669) |
| LIC, mean (SD), mg/g dw | 12.0 (14.8) | 10.1 (11.5) |
| > 7 mg/g dw, n (%) | 103 (46.0) | 45 (40.2) |
| Myocardial iron by T2* MRI, mean (SD), ms | 33.5 (16.2) | 34.8 (10.7) |

[a]Data on endocrine function were not collected. [b]Defined as the mean of all documented pre-transfusion Hb values during the 24 weeks prior to first dose for each patient.
dw, dry weight; Hb, haemoglobin; ITT, intent to treat; LIC, liver iron concentration; RBC, red blood cell; SD, standard deviation; T2* MRI, T2-weighted magnetic resonance imaging.

**Figure 2. Achievement of RBC transfusion reduction in ITT population**



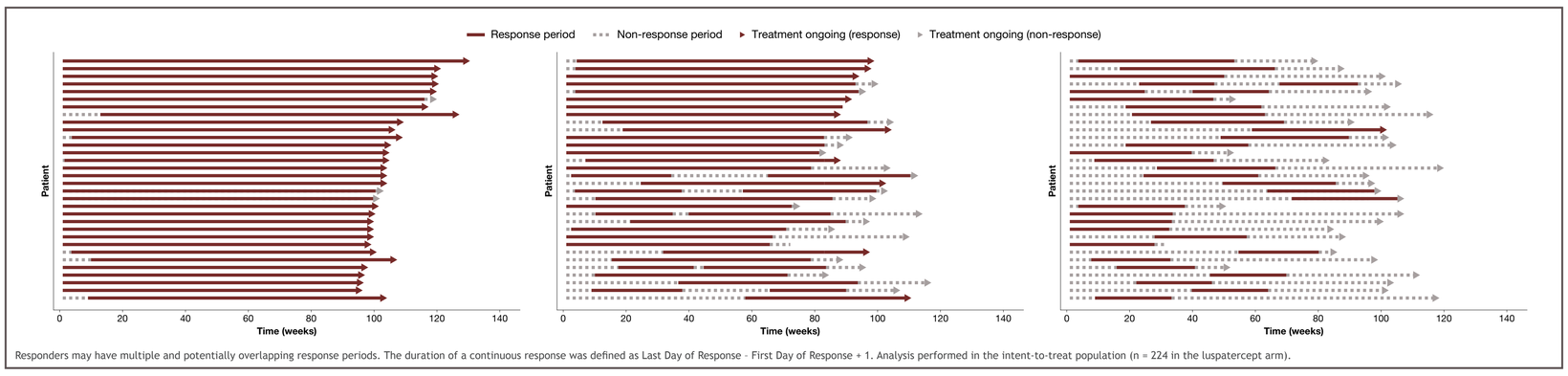

ITT, intent to treat; RBC, red blood cell.

**Table 2. Individual 24-week response periods of ≥ 33% reduction in transfusion burden**

| Separate Responses,[a] n (%) | Luspatercept (N = 224[b]) |
|---|---|
| ≥ 1 | 101 (45.1) |
| ≥ 2 | 74 (33.0) |
| ≥ 3 | 60 (26.8) |
| ≥ 4 | 41 (18.3) |
| ≥ 5 | 33 (14.7) |

[a]All durations of continuous responses were counted regardless of their being overlapping or non-overlapping. [b]While 224 patients were randomised to the luspatercept arm, only 223 patients were treated with luspatercept.

**Figure 3. Response periods for patients in luspatercept arm achieving ≥ 33% reduction in transfusion burden over any 24 weeks**




Responders may have multiple and potentially overlapping response periods. The duration of a continuous response was defined as Last Day of Response − First Day of Response + 1. Analysis performed in the intent-to-treat population (n = 224 in the luspatercept arm).

### Duration of clinical benefit

- Median duration of clinical benefit for luspatercept responders was 76.3 weeks (**Table 3**); luspatercept responders were on treatment for a median of 98.7 weeks (range 30.1–128.1)
- 39 (17.4%) patients randomised to the luspatercept arm had an ongoing clinical benefit response throughout the entire study period from the time of first dose (**Table 3**)

### Safety

- The safety population consisted of 223 patients in the luspatercept arm and 109 in the placebo arm
- Adverse events (AEs) occurring more frequently in the luspatercept arm versus the placebo arm included bone pain, arthralgia, and dizziness (**Table 4**)
  - New onset of these AEs decreased over time during the study (**Figure 4**)
  - Patients who crossed over from the placebo to the luspatercept arm had similar rates of incidence and discontinuation due to these AEs, compared with patients who were initially randomised to the luspatercept arm
- Bone pain, arthralgia, and dizziness were largely transient, grade 1–2, not associated with dose level, and not associated with treatment modification or discontinuation

**Table 3. Duration of clinical benefit for luspatercept-treated patients**

| Characteristic | Luspatercept (N = 224[a]) |
|---|---|
| Patients achieving clinical benefit,[b] n (%) | 101 (45.1) |
| Duration of clinical benefit, median (range), weeks | 76.3 (24.0-128.1) |
| Patients with no loss of response, n (%) | 39 (17.4) |
| Patients achieving RBC-TI, n (%) | |
| RBC-TI ≥ 8 weeks | 25 (11.2) |
| RBC-TI ≥ 24 weeks | 5 (2.2) |
| RBC-TI ≥ 48 weeks | 3 (1.3) |
| Duration of RBC-TI, median (range), weeks | |
| Duration of response in patients achieving RBC-TI ≥ 8 weeks | 10.6 (8.0-106.3) |
| Duration of response in patients achieving RBC-TI ≥ 24 weeks | 94.6 (32.1-106.3) |
| Duration of response in patients achieving RBC-TI ≥ 48 weeks | 100 (94.6-106.3) |
| Mean reduction in RBC units transfused in clinical benefit responders vs baseline,[c] RBC units (U per week) | |
| Reduction in any 24 week period | 6.69 (0.28) |
| Patients with > 15 RBC U/24 weeks at baseline | 8.36 (0.35) |

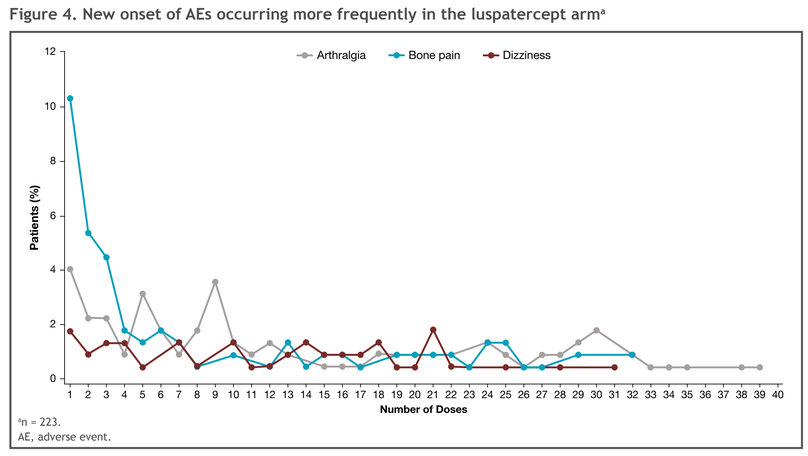
[a]Luspatercept intent-to-treat population. [b]Clinical benefit was defined as the time of first response (≥ 33% reduction in RBC transfusion over any 24 weeks) to discontinuation due to any cause at that episode. [c]For each patient, the 24 week period in which they received the fewest RBC transfusions was counted.
RBC, red blood cell; TI, transfusion independence.

**Table 4. AEs occurring more frequently in the luspatercept arm**

| AEs | Luspatercept (n = 223[a]) | Placebo (n = 109[b]) |
|---|---|---|
| Bone pain, n (%) | | |
| Incidence | 45 (20.2) | 9 (8.3) |
| Discontinuation due to bone pain | 1 (0.4) | 0 |
| Arthralgia, n (%) | | |
| Incidence | 47 (21.1) | 16 (14.7) |
| Discontinuation due to arthralgia | 2 (0.9) | 0 |
| Dizziness, n (%) | | |
| Incidence | 27 (12.1) | 5 (4.6) |
| Discontinuation due to dizziness | 0 | 0 |

[a]Luspatercept safety population. [b]Placebo safety population.
AE, adverse event.

**Figure 4. New onset of AEs occurring more frequently in the luspatercept arm[a]**

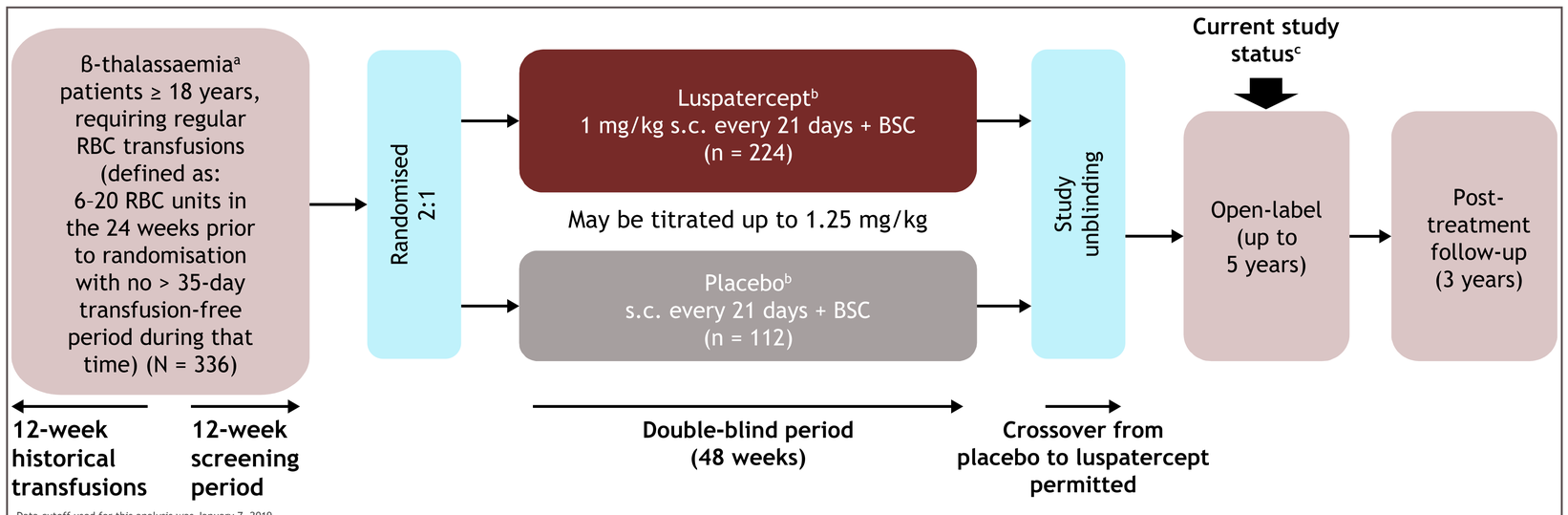



[a]n = 223.
AE, adverse event.

## Conclusions

- Most patients with ß-thalassaemia who achieved clinical benefit with luspatercept experienced multiple episodes of clinically meaningful transfusion burden reduction and had durable clinical benefit over the follow-up period
- The incidence of AEs with luspatercept was consistent with the previously reported 48-week safety profile, was not associated with dose level, and decreased over time with no impact on treatment modification or continuation
- Patients continue to be monitored for safety outcomes[7]
- BEYOND is an ongoing phase 2 study to determine the efficacy and safety of luspatercept in patients with non-transfusion-dependent ß-thalassaemia (NCT03342404)
- A phase 2a study is currently ongoing to evaluate the safety and pharmacokinetics of luspatercept in paediatric transfusion-dependent ß-thalassaemia patients (NCT04143724)

**Figure 1. Study design of the BELIEVE trial**




Data cutoff used for this analysis was January 7, 2019.
[a]ß-thalassaemia or Hb E/ß-thalassaemia (compound ß-thalassaemia with mutation and/or multiplication of α-globin genes was allowed). [b]Patients could receive RBC transfusions and ICT to maintain their baseline Hb level. [c]The trial is fully enrolled and patients continue to receive treatment or follow-up.
BSC, best supportive care; Hb, haemoglobin; ICT, iron chelation therapy; RBC, red blood cell; s.c., subcutaneously.

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## Disclosures

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