Benefit of continuing therapy with luspatercept in patients with ß-thalassemia who do not achieve ≥ 33% reduction in red blood cell transfusion burden in weeks 13-24 in the BELIEVE trial

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Introduction

- ß-thalassemia is characterized by anemia and ineffective erythropoiesis[1]
- Red blood cell (RBC) transfusions are the basis of effective anemia treatment but may result in progressive iron overload and iron-related complications[2]
- Luspatercept is a first-in-class erythroid maturation agent that enhances late-stage erythropoesis[3]
- In the phase 3, double-blind, placebo-controlled BELIEVE trial (NCT02604433), luspatercept provided significantly greater reductions in RBC transfusion burden than placebo for adults with ß-thalassemia[4]
  - Patients who did not achieve ≥ 33% reduction from baseline in RBC transfusion burden during weeks 13-24 (≥ 2 RBC units; the primary efficacy endpoint of the BELIEVE trial) were classified as luspatercept non-responders
- We explored the potential clinical benefit of continuing treatment after week 24 among luspatercept non-responders

Objective

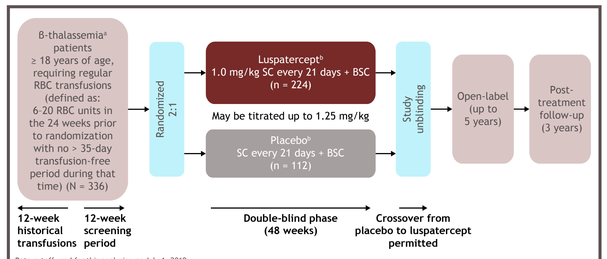
- To evaluate the benefit of continuing luspatercept therapy in luspatercept non-responders in the BELIEVE trial

Methods

Study design

- The BELIEVE trial study design is shown in **Figure 1**

Figure 1. Study design of the BELIEVE trial



Data cutoff used for this analysis was July 1, 2019.
[a]ß-thalassemia or Hb E/ß-thalassemia (compound ß-thalassemia 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.
BSC, best supportive care; Hb, hemoglobin; ICT, iron chelation therapy; SC, subcutaneously.

- Patients with ß-thalassemia were randomized 2:1 to receive luspatercept 1.0 mg/kg or placebo every 3 weeks for 48 weeks during the double-blind period
- The primary endpoint was ≥ 33% reduction from baseline in RBC transfusion burden during weeks 13-24 (≥ 2 RBC units)

Luspatercept non-responders

- In the BELIEVE trial, luspatercept non-responders were defined as patients who did not achieve a reduction in RBC transfusion burden of ≥ 33% from baseline during weeks 13-24 (≥ 2 RBC units)
  - These patients could continue luspatercept treatment beyond week 25 and were followed for the entire treatment period (data cutoff: July 2019)

Analyses

- RBC transfusion burden was analyzed for the week-25 to -48 follow-up period and for the entire treatment period
- Changes from baseline in RBC transfusion units and visits between placebo and luspatercept non-responders or luspatercept responders were analyzed as least squares mean (LSM) differences (with 95% CI) based on analysis of covariance (ANCOVA) models with geographic regions defined at randomization and baseline transfusion burden as covariates
- RBC transfusion independence (TI) was defined as the absence of any RBC transfusion during a rolling 8-week time interval during the entire study period
  - Odds ratio (luspatercept over placebo) with 95% CI and *P* values were estimated from the Cochran-Mantel-Haenszel test stratified by geographic location at randomization
- Changes from baseline in serum ferritin (SF) levels were based on categories of baseline SF ≥ 1000 µg/L to post-baseline < 1000 µg/L and baseline ≥ 2500 µg/L to post-baseline < 2500 µg/L

Results

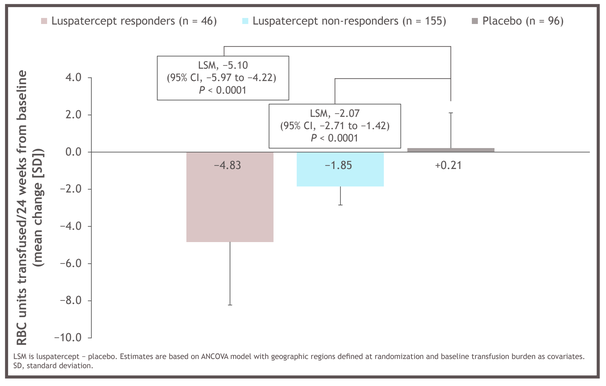
Patients

- The intent-to-treat population of the BELIEVE trial comprised 336 patients; 224 patients were randomized to the luspatercept arm and 112 to the placebo arm
- Of the 224 patients randomized to luspatercept, 47 (21%) were defined as luspatercept responders for this analysis
- In total, 177 (79%) patients were defined as luspatercept non-responders, of whom 163 continued treatment in weeks 25-48

Transfusion burden: weeks 25-48 versus baseline

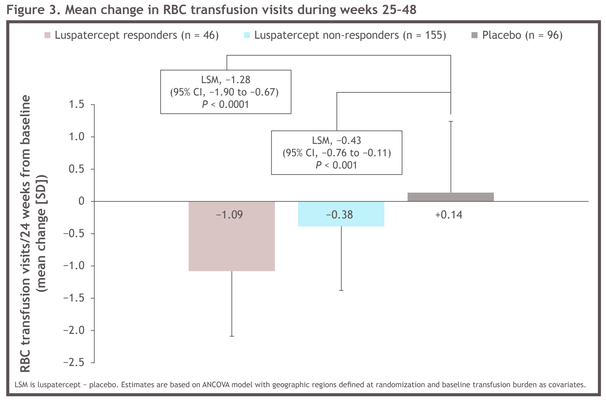
- Of the 163 luspatercept non-responders at weeks 13-24 who continued treatment, 112 (68.7%) achieved a subsequent reduction in the number of RBC units transfused versus 26/97 (26.8%) patients in the placebo arm
- **RBC units transfused:** luspatercept non-responders had a mean change from baseline in RBC units transfused of −1.85 RBC units/24 weeks, versus +0.21 RBC units/24 weeks for patients who received placebo (**Figure 2**)
- **RBC transfusion visits:** luspatercept non-responders had a mean change from baseline in RBC transfusion visits of −0.38 RBC visits/24 weeks, versus +0.14 RBC visits/24 weeks for patients who received placebo (**Figure 3**)

Figure 2. Mean change in RBC units transfused for luspatercept responders, non-responders, and placebo-treated patients during weeks 25-48



LSM is luspatercept − placebo. Estimates are based on ANCOVA model with geographic regions defined at randomization and baseline transfusion burden as covariates.
SD, standard deviation.

Figure 3. Mean change in RBC transfusion visits during weeks 25-48

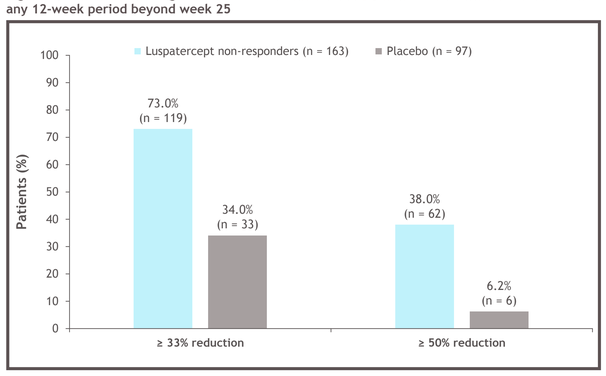


LSM is luspatercept − placebo. Estimates are based on ANCOVA model with geographic regions defined at randomization and baseline transfusion burden as covariates.

Transfusion burden: entire treatment period

- In any 12-week period during the entire treatment period, 119/163 (73.0%) luspatercept non-responders achieved ≥ 33% reduction in RBC units transfused versus 33/97 (34.0%) patients who received placebo (**Figure 4**)
  - Of 163 luspatercept non-responders, 62 (38.0%) achieved ≥ 50% reduction in RBC units transfused versus 6/97 (6.2%) patients who received placebo
- During any 8-week interval, 8/163 (4.9%) luspatercept non-responders achieved RBC-TI versus 1/97 (1.0%) patients who received placebo (odds ratio, 5.28 [95% CI, 0.63-44.16]; *P* = 0.1)

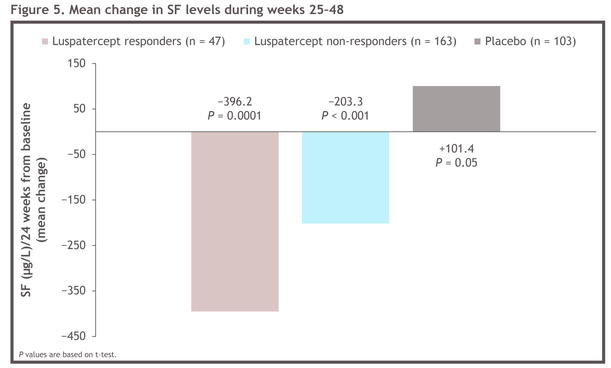
Figure 4. Patients achieving ≥ 33% or ≥ 50% reduction in RBC transfusion units from baseline in any 12-week period beyond week 25



SF: weeks 25-48

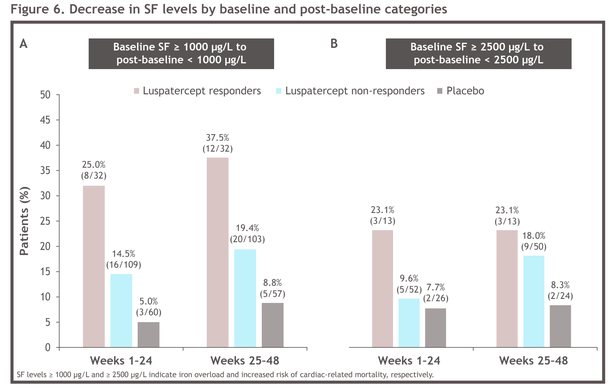
- 97/163 (59.5%) luspatercept non-responders achieved a reduction in SF from baseline versus 63/97 (37.1%) patients who received placebo
- For luspatercept non-responders, the mean change in SF from baseline was −203.3 µg/L (−8.1%) (**Figure 5**)
- Of 103 luspatercept non-responders with baseline mean SF level ≥ 1000 µg/L, 20 (19.4%) achieved post-baseline mean SF level < 1000 µg/L during weeks 25-48 (**Figure 6A**)
- Of 50 luspatercept non-responders with baseline mean SF level ≥ 2500 µg/L, 9 (18.0%) achieved post-baseline mean SF level < 2500 µg/L during weeks 25-48 (**Figure 6B**)

Figure 5. Mean change in SF levels during weeks 25-48



P values are based on t-test.

Figure 6. Decrease in SF levels by baseline and post-baseline categories



SF levels ≥ 1000 µg/L and ≥ 2500 µg/L indicate iron overload and increased risk of cardiac-related mortality, respectively.

Conclusions

- Most patients with ß-thalassemia identified as non-responders to luspatercept treatment in weeks 13-24 in the BELIEVE trial received clinical benefit from continuing therapy
  - These patients had greater reductions in RBC transfusion units and visits and in SF levels than patients receiving placebo throughout the randomized treatment period
- Continued treatment with luspatercept even in patients not showing an initial full response may provide clinical benefits and reduced healthcare resource use over a longer period

References

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