Longitudinal effect of luspatercept treatment on iron overload and iron chelation therapy in adult patients with ß-thalassemia in the BELIEVE trial

Olivier Hermine,[1,2] Maria Domenica Cappellini,[3] Ali T. Taher,[4] Thomas D. Coates,[5,6] Vip Viprakasit,[7] Ersi Voskaridou,[8] Ashutosh Lal,[9] Hong Keng Liew,[10] Silverio Perrotta,[11] Abderrahim Khelif,[12] Antonis Kattamis,[13] Jeevan K. Shetty,[14] George Zhang,[15] Yu (Olivia) Tian,[15] Dimana Miteva,[14] Tatiana Zinger,[14] Derek Tang,[15] Jay T. Backstrom,[16] John B. Porter[17]

[1]Imagine Institute, INSERM U1163, University of Paris, Paris, France; [2]Department of Hematology, Necker Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [3]Fondazione IRCCS Ca' Granda Policlinico Hospital, University of Milan, Milan, Italy; [4]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; [5]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA; [6]USC Keck School of Medicine, Los Angeles, CA; [7]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [8]Thalassemia and Sickle Cell Center of Laiko General Hospital, Athens, Greece; [9]University of California San Francisco, Benioff Children's Hospital, Oakland, CA; [10]Hospital Sultanah Bahiyah, Alor Setar, Malaysia; [11]Università della Campania, Luigi Vanvitelli, Caserta, Italy; [12]Farhat Hached Teaching Hospital, Sousse University, Tunisia; [13]First Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece; [14]Celgene International, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Bristol Myers Squibb, Princeton, NJ; [16]Acceleron Pharma, Cambridge, MA; [17]University College London, University College London Hospitals, London, UK

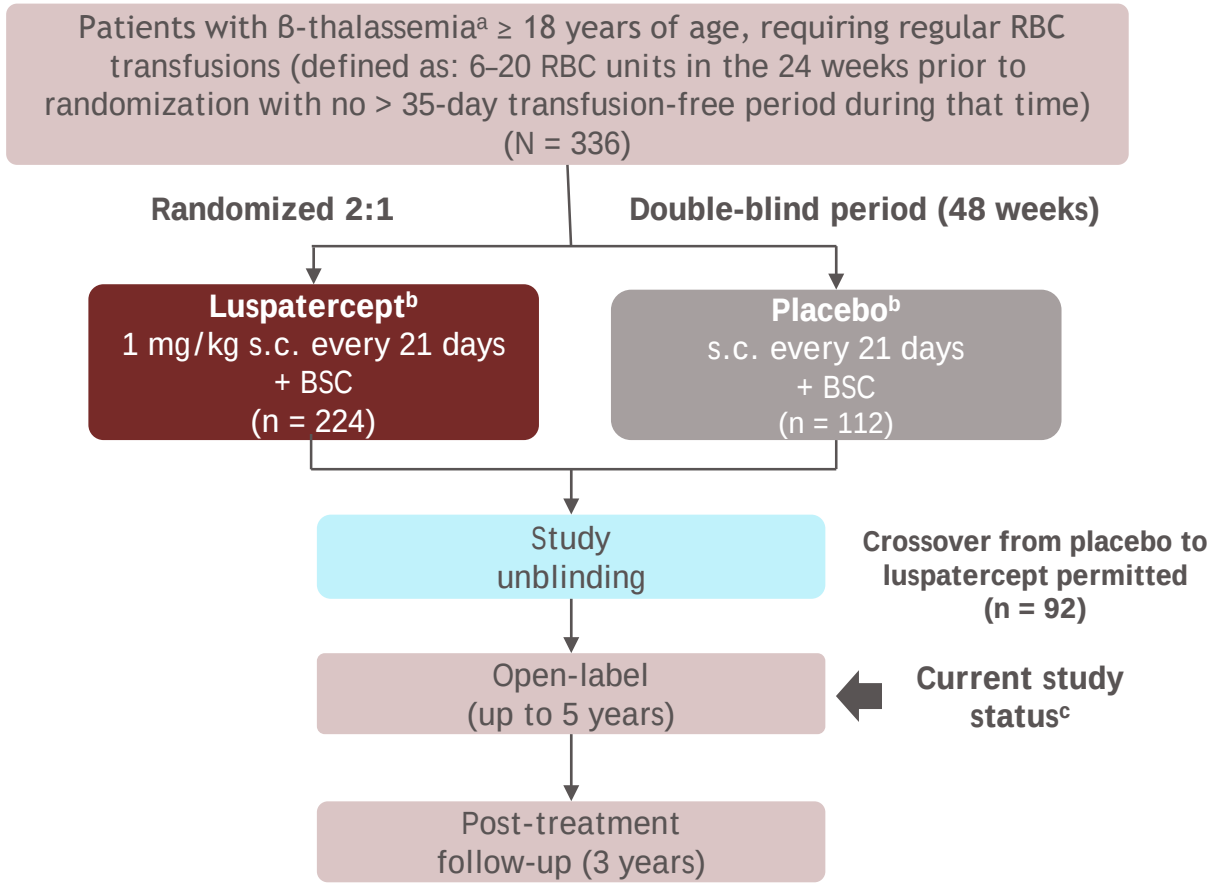
Presenting author disclosures

O.H.: Roche – consultancy; BMS – consultancy, research funding; AB Science – consultancy, current equity holder in publicly-traded company, honoraria, patents, royalties, research funding; Alexion, Novartis - research funding.

Introduction

- RBC transfusions are the main supportive treatment for chronic anemia due to ß-thalassemia[1]
  - Transfusion-dependent patients require ICT to prevent iron overload from RBC transfusions and associated complications[2]
- Thus, there is a clinical need to reduce transfusions and iron burden in patients with anemia due to ß-thalassemia
- Luspatercept, a first-in-class erythroid maturation agent, is approved by the US Food and Drug Administration for the treatment of anemia in adult patients with ß-thalassemia requiring regular RBC transfusions[3–6]
- This analysis assessed the effect of long-term luspatercept use on iron loading and ICT use in the phase 3 BELIEVE trial (NCT02604433)[7]

Figure 1. BELIEVE study trial design



[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 to maintain their baseline Hb level and ICT. [c]The trial is fully enrolled and patients continue to receive treatment or follow-up.
BSC, best supportive care; Hb, hemoglobin; ICT, iron chelation therapy; RBC, red blood cell; s.c., subcutaneously.

1. Taher AT, et al. *Lancet* 2018;391:155–167. 2. Taher AT, Cappellini MD. *Blood* 2018;132:1781–1791. 3. Suragani RNVS, et al. *Blood* 2014;123:3864–3872. 4. Attie KM, et al. *Am J Hematol* 2014;89:766–770. 5. Piga A, et al. *Blood* 2019;133:1279–1289. 6. Reblozyl (luspatercept-aamt) [package insert]. Summit, NJ: Celgene Corporation; April 2020. 7. Cappellini MD, et al. *N Engl J Med* 2020;382:1219–1231.

Results

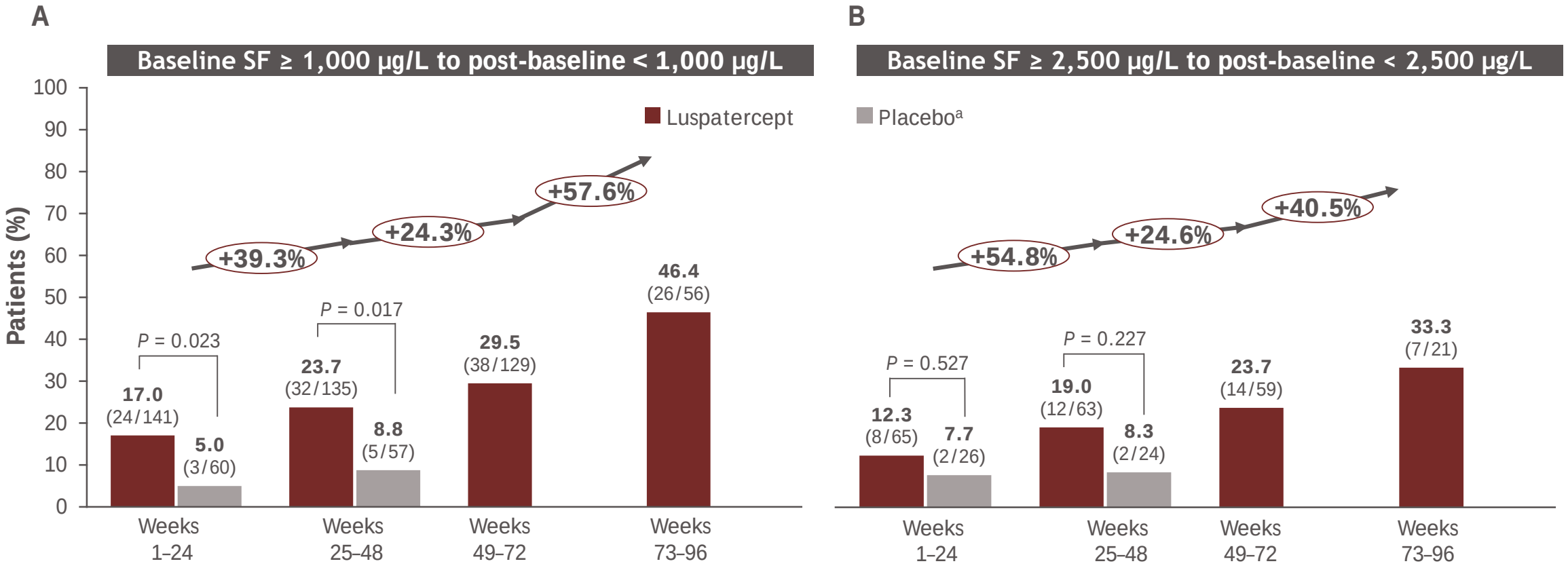
Table. Patient baseline characteristics

Characteristic	Luspatercept (N = 224)	Placebo (N = 112)
Age, median (range), years	30 (18–66)	30 (18–59)
Female, n (%)	132 (58.9)	63 (56.3)
Hb (24 weeks),[a] 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)
SF, mean (SD), µg/L	2,097 (1,757)	1,845 (1,669)
LIC, mean (SD), mg/g dw > 3 mg/g dw, n (%)	12.0 (14.8) 154 (68.8)	10.1 (11.5) 75 (67.0)
Myocardial iron by T2* MRI, mean (SD), ms	33.5 (16.2)	34.8 (10.7)
ICT use[b,c], n (%)		
Deferasirox	139 (62.3)	63 (57.8)
Deferiprone	92 (41.3)	40 (36.7)
Deferoxamine mesylate / deferoxamine	83 (37.2)	39 (35.8)

[a]Defined as the mean of all documented pre-transfusion Hb values during the 24 weeks prior to first dose for each patient. [b]Defined as started before the start of study treatment and either ended before the start of the study treatment or continued after study treatment. [c]Analyzed using the safety population (luspatercept n = 223, placebo n = 109).
dw, dry weight; LIC, liver iron concentration; SD, standard deviation; SF, serum ferritin; T2* MRI, T2-weighted magnetic resonance imaging.

Results (cont.)

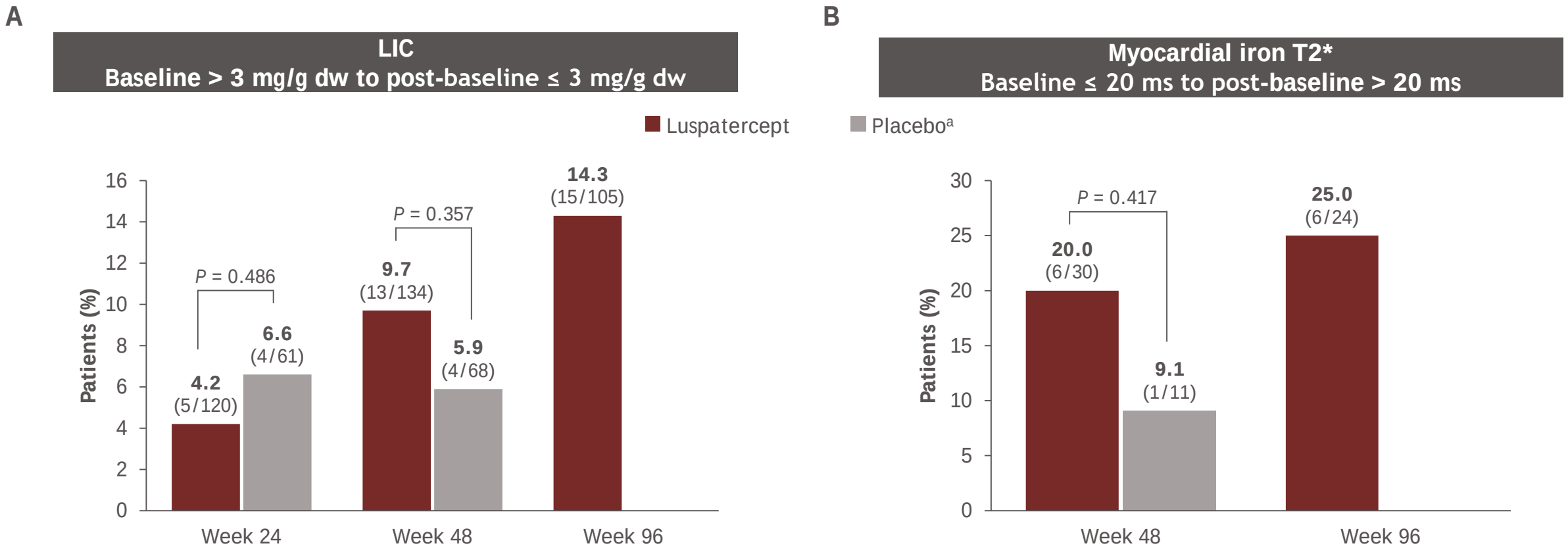
Figure 2. Decrease in SF categories baseline ≥ 1,000 µg/L to post-baseline < 1,000 µg/L (A) and baseline ≥ 2,500 µg/L to post-baseline < 2,500 µg/L (B)



Data cutoff: July 1, 2019.
P values are estimated from Cochran-Mantel-Haenszel test. SF levels ≥ 1,000 µg/L and ≥ 2,500 µg/L indicate iron overload and increased risk of cardiac-related mortality, respectively.
[a]Placebo patients evaluated up to Week 48.

Results (cont.)

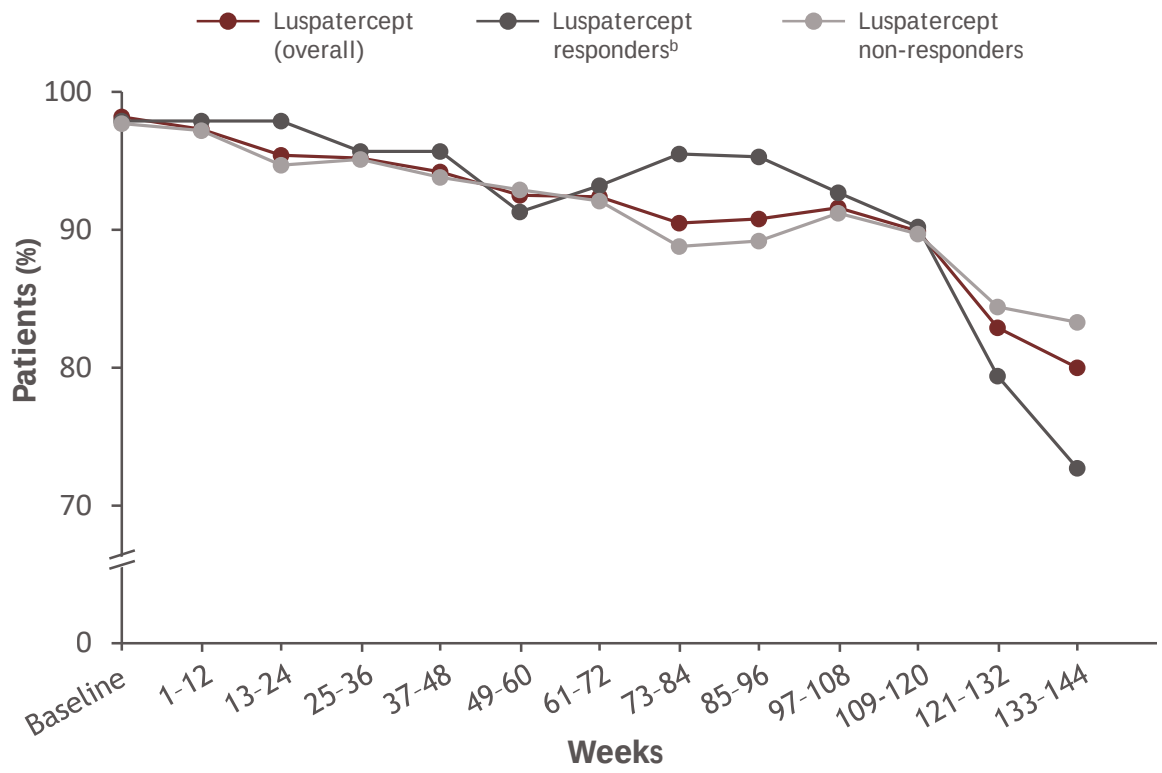
Figure 3. Decrease in LIC (A) and myocardial iron T2* categories (B)



Data cutoff: July 1, 2019.
P values are estimated from Cochran–Mantel–Haenszel test. Patients with LIC ≥ 3 mg/g dw are considered to have iron overload. Myocardial iron T2* < 20 ms indicates increased cardiac risk.
[a]Placebo patients evaluated up to Week 48.

Results (cont.)

Figure 4. Luspatercept-treated patients receiving ≥ 1 ICT over time[a]



	Baseline	1-12	13-24	25-36	37-48	49-60	61-72	73-84	85-96	97-108	109-120	121-132	133-144
Overall	219	217	207	200	195	186	169	161	148	142	133	92	28
Responders	46	46	46	45	44	42	41	42	41	38	37	27	8
Non-responders	173	171	161	155	151	144	128	119	107	104	96	65	20

- The mean (SD) daily dose of deferasirox in all luspatercept-treated patients at baseline was 1,332.37 mg (1,087.0)
- During Weeks 85–96, the mean change (SD) in daily dose of deferasirox from baseline in the luspatercept arm overall (n = 118), responders (n = 32), and non-responders (n = 86) was −189.8 mg (768.5), −201.1 mg (740.2), and −185.6 mg (783.0), respectively
- The mean change (SD) in the luspatercept arm overall at Week 144 (n = 25) was −810.1 mg (1,614.8)

Data cutoff: July 1, 2019.
Only a small number of patients could be evaluated at the later time points due to poor tracking and ICT adherence.
[a]Includes only patients initially randomized to receive luspatercept. [b]Responders are defined as patients achieving ≥ 33% reduction in transfusion burden during Weeks 13–24, with a reduction of ≥ 2 RBC units, versus baseline.

Summary

- A significant number of luspatercept-treated patients with baseline SF ≥ 1,000 µg/L shifted to SF < 1,000 µg/L during the first 48 weeks
- The proportion of patients receiving ≥ 1 ICT gradually declined in both luspatercept responders and non-responders over time up to Week 144
- Both luspatercept responders and non-responders experienced decreases in mean daily dose of deferasirox over time

Acknowledgments

- The study was supported by Celgene, a Bristol-Myers Squibb Company, in collaboration with Acceleron Pharma
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Jacqueline Moy, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

Email: ohermine@gmail.com