Reblozyl® (Luspatercept)

How it works and what studies have shown
Supportive material for TIF's global patients' community

Prepared by Thalassaemia International Federation (TIF)

THALASSAEMIA
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FEDERATION

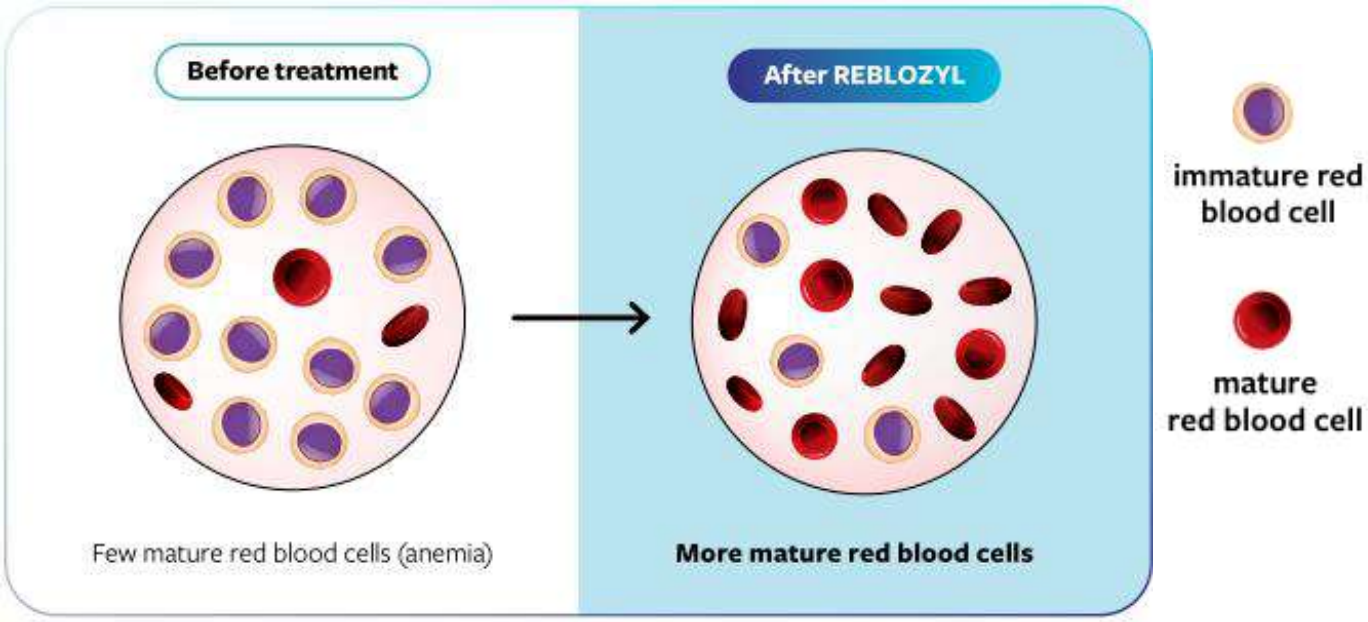
CONTENTS

INTRODUCTION - BASIC INFORMATION

REBLOZYL® is the first and only erythroid maturation agent

- REBLOZYL® is called an erythroid maturation agent because it helps erythroid cells develop and become mature, working red blood cells. This may result in patients who receive the drugs in a greater number of healthy red blood cells and improve thus anemia (see figure 1).

Figure 1.



Source: REBLOZYL PATIENT BROCHURE https://www.reblozyl.com/resources-support-bt/

Why people with thalassaemia (transfusion dependent (TD) have too few mature, working Red Blood Cells (RBCs)

Mature Red Blood Cells (RBCs) are produced through a process called erythropoiesis. In people with this disorder, not enough erythroid immature cells are able to mature and leave the bone marrow. These erythroid cells are unable to do the job of fully working, mature red blood cells, which is to carry oxygen throughout the body.

When erythroid cells start to pile up in the bone marrow, they can prevent mature, working red blood cells from developing

The term for when red blood cells are unable to fully mature or develop before leaving the bone marrow is "**ineffective erythropoiesis**"

- This low production of mature working red blood cells leads to low levels of hemoglobin and symptoms of anemia

What causes β-thalassemia?

In people with β-thalassemia, hemoglobin may not be made correctly. Normal, healthy hemoglobin includes 2 sets of 2 different proteins: an alpha and a beta. In many people with β-thalassemia, "beta globin" proteins are not formed correctly. If your body does not produce enough of either protein, red blood cells do not form properly and cannot carry the oxygen your organs need to stay healthy. This could result in anemia, which may be severe enough to require red blood cell transfusions.

Lack of mature RBCs i.e. ineffective production of normal, mature RBCs, that can perform their role effectively i.e. carrying the oxygen to our cells, tissues and organs for their normal growth and functioning, is what occurs in β-thalassaemia major consequent to the defect at the gene controlling the production of the haemoglobin molecule .This is a result of the genetic change or mutation that occurs at the level of the gene responsible for the production of normal haemoglobin.

Reblozyl® (luspatercept-aamt) has received, after many years of clinical trials, approval for use in transfusion dependent β-thalassaemia from the major global regulatory authorities, the **Food and Drug Administration (FDA) in the USA, on 8 November 2019, followed by the European Medicines Agency (EMA) on 25 June 2020.**

In addition, the FDA has recently accepted for priority review the supplemental Biologics License Application (sBLA) for Reblozyl® (luspatercept-aamt), for the treatment of anaemia in adults with non-transfusion dependent (NTD) beta-thalassaemia. The FDA has set Prescription Drug User Fee Act (PDUFA) goal date of March 27, 2022.

Priority Review is a programme of the FDA that ensures the quick assessment of drugs that are intended to treat a serious disease or condition, for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies.

EMA's Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment of the application and gives a recommendation **(Positive/Negative Opinion)** on whether the medicine should be marketed or not. However, the **European Commission is the authorising body for all centrally authorised medicinal products,** who takes a legally binding decision based on EMA's recommendation.

In addition EMA has validated the type II variation for Reblozyl® in non-transfusion dependent thalassaemia (NTDT).

CLINICAL TRIALS - What has been demonstrated

Key information on findings from Phase 2

Phase 2 Clinical Trial (NCT01749540<https://clinicaltrials.gov/ct2/show/NCT01749540>)

Started: 11 February 2013 and
Ended: 11 November 2015

The results were submitted to clinicaltrials.gov on the 14th of December 2016

The trial included transfusion dependent (TD) and non-transfusion dependent (NTDT) patients who received subcutaneous injections every 21days/3 weeks

- In TD patients the PRIMARY ENDPOINT was to achieve a ≥20% reduction of the transfusion burden (from baseline) and this was **achieved in 81% of TD patients**

- In NTDT patients the PRIMARY ENDPOINT was to achieve an increase of haemoglobin level of ≥1.5g/dl and this was **achieved in 58% of the patients**

These results prompted the design of the Phase 3 clinical trial – referred to as the BELIEVE Trial. It is a randomized double-blind, placebo controlled study conducted for **at least 48 weeks.**

Key information on Phase 3 - BELIEVE Trial

Phase3
NCT02604433<https://clinicaltrials.gov/ct2/show/results/NCT02604433?term=luspatercept&cond=thalassemia&draw=2&rank=5>)

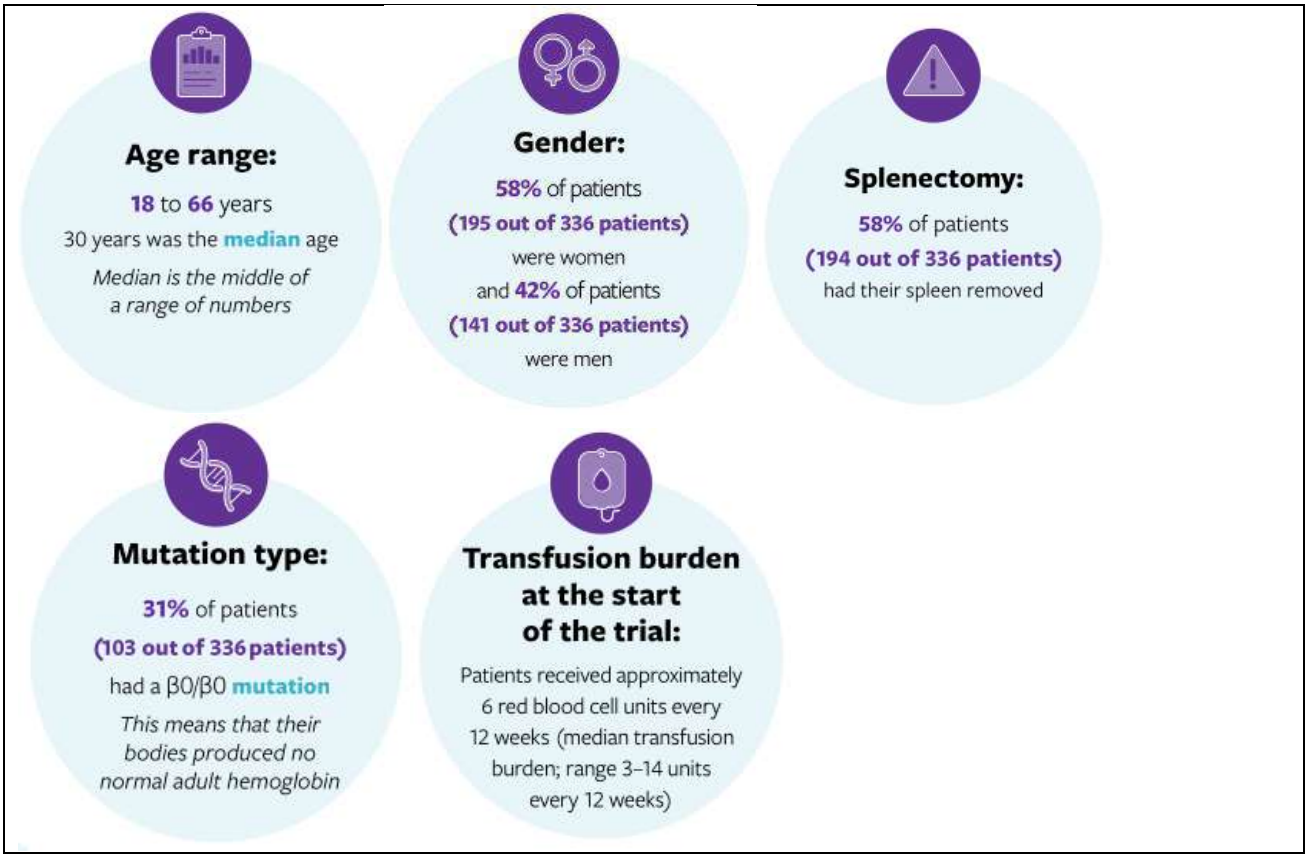
Started on the 2nd of May 2016 with
a) Primary Endpoint cut-off date: 24 November 2017
b) Secondary Endpoints cut-off date: 11 May 2018

Results were submitted to clinicaltrials.gov: 06 December 2019

Eligible patients ≥18 years, β-thal or HbE/ β-thal requiring transfusions of 6-20 Red Blood Cells (RBCs) with no transfusion free period of >35 days within 24 weeks PRIOR to randomization.
Starting dose: 1.0mg/kg of body weight with filtration up to 1.25mg/kg according to the protocol

The trial was performed at 65 sites in 15 countries. Median age 30 years (see figures 2 & 3)

Figure 2.



Source: REBLOZYL PATIENT BROCHUREhttps://www.reblozyl.com/resources-support-bt

More details on ages, genotypes, clinical/disease and other demographic characteristics are shown below in figure 3.

Figure 3.

Table 1. Baseline Demographic and Disease Characteristics.*

Characteristic	Luspatercept Group (N = 224)	Placebo Group (N = 112)	Total (N = 336)
Median age (range) — yr	30 (18–66)	30 (18–59)	30 (18–66)
Female sex — no. (%)	132 (58.9)	63 (56.3)	195 (58.0)
Geographic region — no. (%)			
North America and Europe	100 (44.6)	51 (45.5)	151 (44.9)
Asia–Pacific	72 (32.1)	35 (31.3)	107 (31.8)
Middle East and North Africa	52 (23.2)	26 (23.2)	78 (23.2)
Diagnosis of hemoglobin E–β-thalassemia — no. (%)	31 (13.8)	21 (18.8)	52 (15.5)
Presence of a β^0/β^0 genotype — no. (%)	68 (30.4)	35 (31.3)	103 (30.7)
Median pretransfusion hemoglobin level (range) — g/dl†	9.3 (4.5–11.4)	9.2 (5.8–11.7)	9.3 (4.5–11.7)
Median transfusion burden (range) — no. of red-cell units in 24 wk‡	14 (6–24)	15 (6–26)	14 (6–26)
Transfusion burden category — no. (%)			
≤10 red-cell units in 24 wk	33 (14.7)	14 (12.5)	47 (14.0)
>10 to ≤15 red-cell units in 24 wk	96 (42.9)	47 (42.0)	143 (42.6)
>15 red-cell units in 24 wk	95 (42.4)	51 (45.5)	146 (43.5)
Previous splenectomy — no. (%)	129 (57.6)	65 (58.0)	194 (57.7)
Mean total bilirubin level — μmol/liter	35.4	35.9	NA
Median liver iron concentration (range) — mg/g of dry liver weight	6.14 (0.8–125.0)	5.05 (0.2–53.2)	5.69 (0.2–125.0)
Liver iron concentration category — no. (%)			
0–3 mg/g of dry liver weight	70 (31.3)	37 (33.0)	107 (31.8)
>3–7 mg/g of dry liver weight	51 (22.8)	30 (26.8)	81 (24.1)
>7–15 mg/g of dry liver weight	38 (17.0)	19 (17.0)	57 (17.0)
>15 mg/g of dry liver weight	65 (29.0)	26 (23.2)	91 (27.1)
Median myocardial iron deposition (range) — msec§	34.7 (3.0–205.9)	36.3 (6.4–57.5)	35.0 (3.0–205.9)
Median serum ferritin level (range) — μg/liter	1441.3 (88.0–6400.0)	1301.5 (136.0–6400.0)	NA
Current iron-chelation therapy — no. (%)¶	222 (99.6)	109 (100.0)	331 (99.7)

* Data on all baseline demographics and disease characteristics, except current iron-chelation therapy, are shown for the intention-to-treat population (all patients who underwent randomization). Percentages may not total 100 because of rounding. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1. NA denotes not available.

† The baseline pretransfusion hemoglobin level in a patient was defined as the median of all documented pretransfusion hemoglobin levels measured in the 24 weeks (12 weeks of historical information plus 12 weeks of prospectively collected run-in data) before the first dose of luspatercept or placebo.

‡ The baseline transfusion burden was defined as the number of red-cell units transfused in the 24 weeks before the first dose of luspatercept or placebo; red-cell units transfused on the day of the first dose of were considered part of the baseline transfusion burden.

§ Myocardial iron deposition was assessed by means of T2*-weighted magnetic resonance imaging (which allows for distortions in the magnetic field due to hemosiderin or ferritin to quantify effective T2); a value higher than 10 msec indicates minimal risk of heart failure.[18]

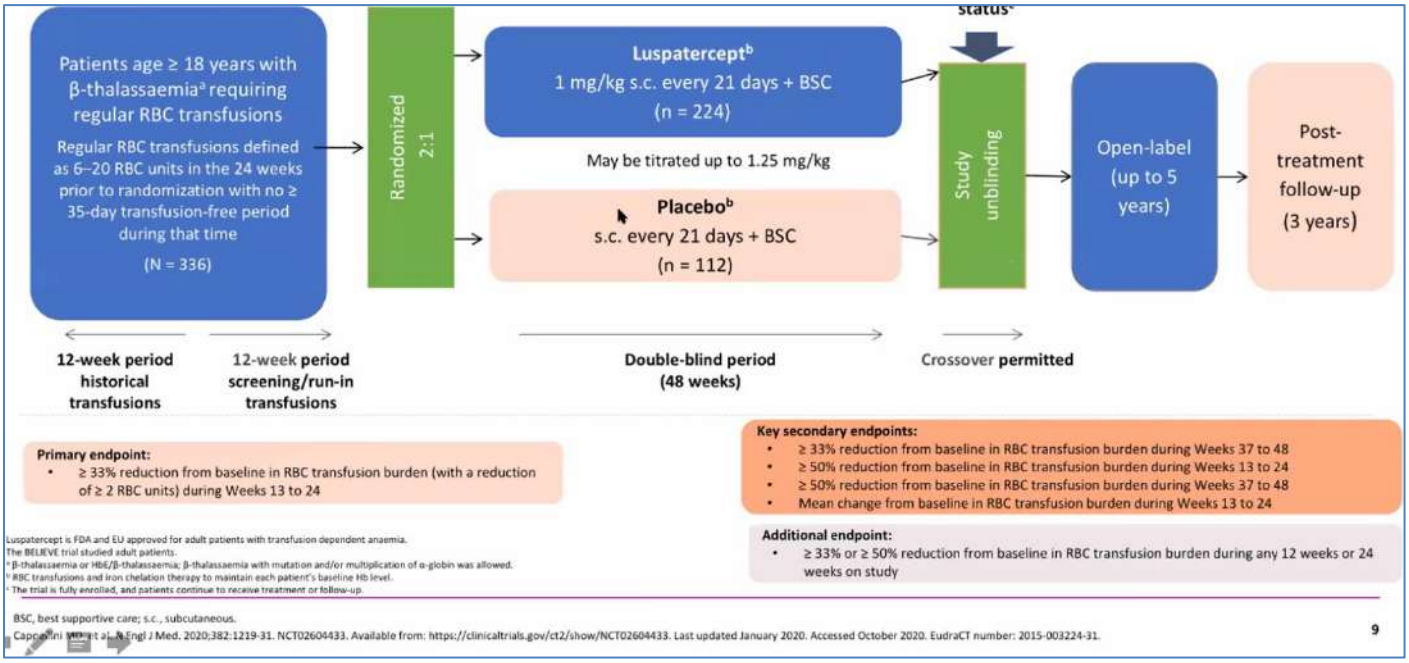
¶ Current iron-chelation therapy was assessed in the safety population (all patients who underwent randomization and received ≥1 dose of luspatercept or placebo — 223 in the luspatercept group and 109 in the placebo group). Combination iron-chelation therapy was permitted.

Source: N Engl J Med 2020;382:1219-31.DOI: 10.1056/NEJMoa1910182

How the BELIEVE Trial (phase 3, randomized, double-blind, placebo-controlled study) was designed is shown below in figure 4.

In the BELIEVE trial, most patients with β-thalassaemia (selected as seen in figure 5) and who did not respond to Luspatercept treatment in weeks 13-24, received meaningful clinical benefit from continuing therapy through week 48 (as seen in figure 7 below) and hence the design of the trial as shown below (figure 4).

Figure 4.



Source: Transcription of (a) Prof. Cappellini's Presentation and (b) Moderated discussion with the panel of International Experts featuring M.D. Cappellini, J. Porter, V. Viprakasit and Y. Aydinok

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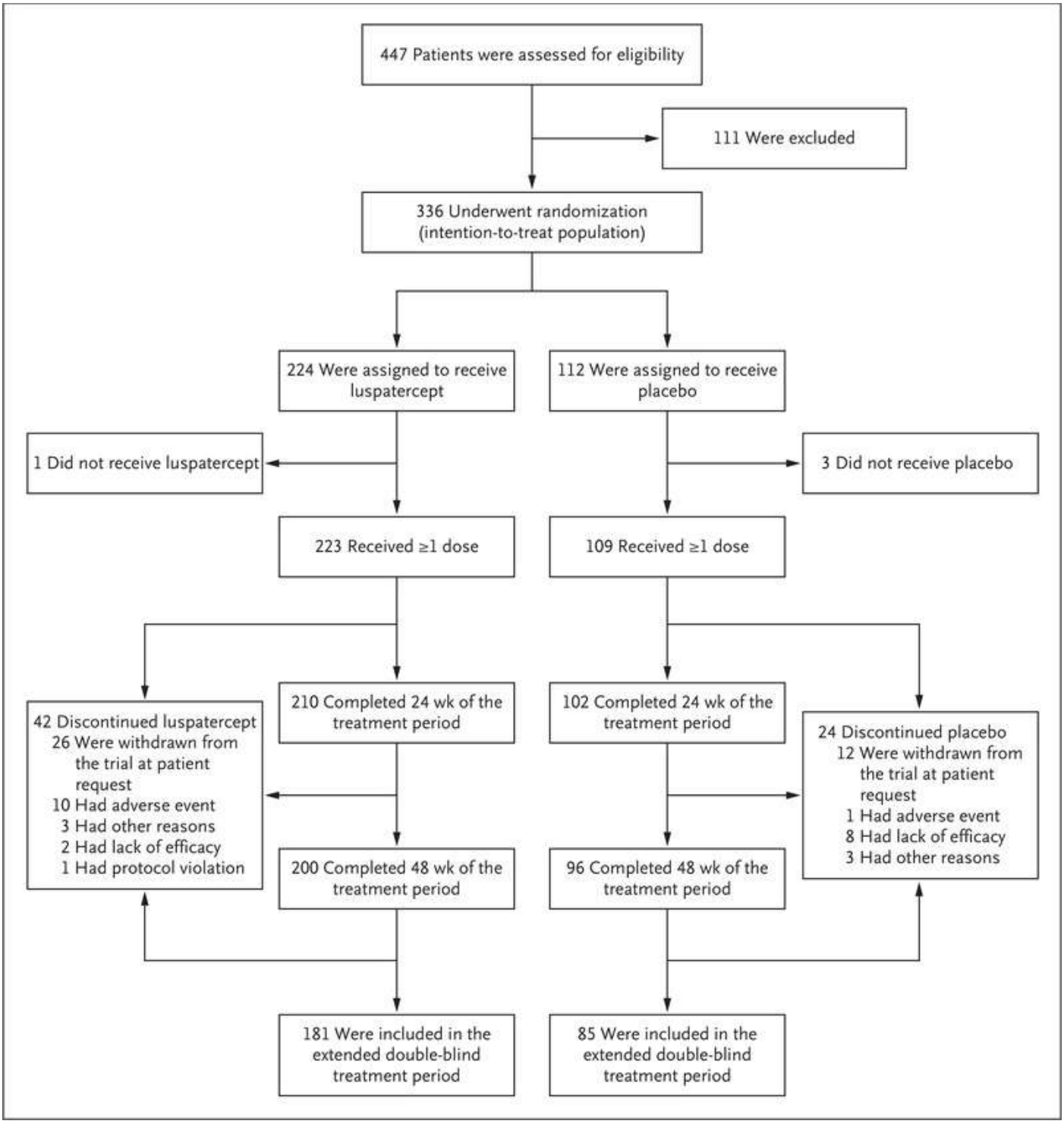
Figure 5 below describes how patients were allocated in the clinical trial studies - Screening, Randomization, and Follow-up.

Figure 5.



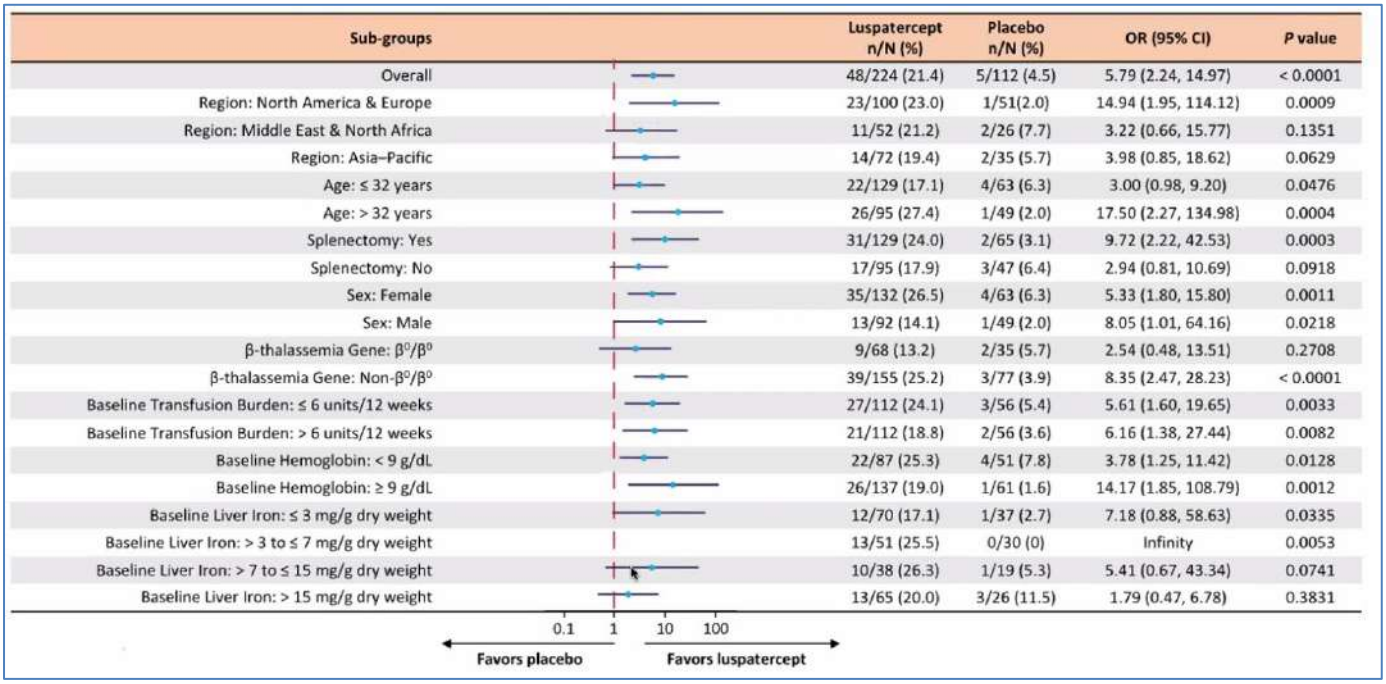
Source: N Engl J Med 2020; 382:1219-1231 DOI: 10.1056/NEJMoa1910182

RESULTS DURING THE FIRST 48 WEEKS ACROSS GENOTYPES

The PRIMARY END POINT was a ≥33% reduction in RBC transfusion burden during weeks 13-24 plus a reduction of at least 2 RBC units over this 12-week interval[1] achieved in 21.4% of the patients (n=48), [figure 7(A)]. Subgroups characteristics are shown in figure 6 below.

177 patients (out of 224) i.e. 79% were non-responders of whom 163 continued treatment in weeks 25-48

Figure 6.



Sub-groups	Luspatercept n/N (%)	Placebo n/N (%)	OR (95% CI)	*P* value
Overall	48/224 (21.4)	5/112 (4.5)	5.79 (2.24, 14.97)	< 0.0001
Region: North America & Europe	23/100 (23.0)	1/51(2.0)	14.94 (1.95, 114.12)	0.0009
Region: Middle East & North Africa	11/52 (21.2)	2/26 (7.7)	3.22 (0.66, 15.77)	0.1351
Region: Asia–Pacific	14/72 (19.4)	2/35 (5.7)	3.98 (0.85, 18.62)	0.0629
Age: ≤ 32 years	22/129 (17.1)	4/63 (6.3)	3.00 (0.98, 9.20)	0.0476
Age: > 32 years	26/95 (27.4)	1/49 (2.0)	17.50 (2.27, 134.98)	0.0004
Splenectomy: Yes	31/129 (24.0)	2/65 (3.1)	9.72 (2.22, 42.53)	0.0003
Splenectomy: No	17/95 (17.9)	3/47 (6.4)	2.94 (0.81, 10.69)	0.0918
Sex: Female	35/132 (26.5)	4/63 (6.3)	5.33 (1.80, 15.80)	0.0011
Sex: Male	13/92 (14.1)	1/49 (2.0)	8.05 (1.01, 64.16)	0.0218
β-thalassemia Gene: β^0/β^0	9/68 (13.2)	2/35 (5.7)	2.54 (0.48, 13.51)	0.2708
β-thalassemia Gene: Non-β^0/β^0	39/155 (25.2)	3/77 (3.9)	8.35 (2.47, 28.23)	< 0.0001
Baseline Transfusion Burden: ≤ 6 units/12 weeks	27/112 (24.1)	3/56 (5.4)	5.61 (1.60, 19.65)	0.0033
Baseline Transfusion Burden: > 6 units/12 weeks	21/112 (18.8)	2/56 (3.6)	6.16 (1.38, 27.44)	0.0082
Baseline Hemoglobin: < 9 g/dL	22/87 (25.3)	4/51 (7.8)	3.78 (1.25, 11.42)	0.0128
Baseline Hemoglobin: ≥ 9 g/dL	26/137 (19.0)	1/61 (1.6)	14.17 (1.85, 108.79)	0.0012
Baseline Liver Iron: ≤ 3 mg/g dry weight	12/70 (17.1)	1/37 (2.7)	7.18 (0.88, 58.63)	0.0335
Baseline Liver Iron: > 3 to ≤ 7 mg/g dry weight	13/51 (25.5)	0/30 (0)	Infinity	0.0053
Baseline Liver Iron: > 7 to ≤ 15 mg/g dry weight	10/38 (26.3)	1/19 (5.3)	5.41 (0.67, 43.34)	0.0741
Baseline Liver Iron: > 15 mg/g dry weight	13/65 (20.0)	3/26 (11.5)	1.79 (0.47, 6.78)	0.3831

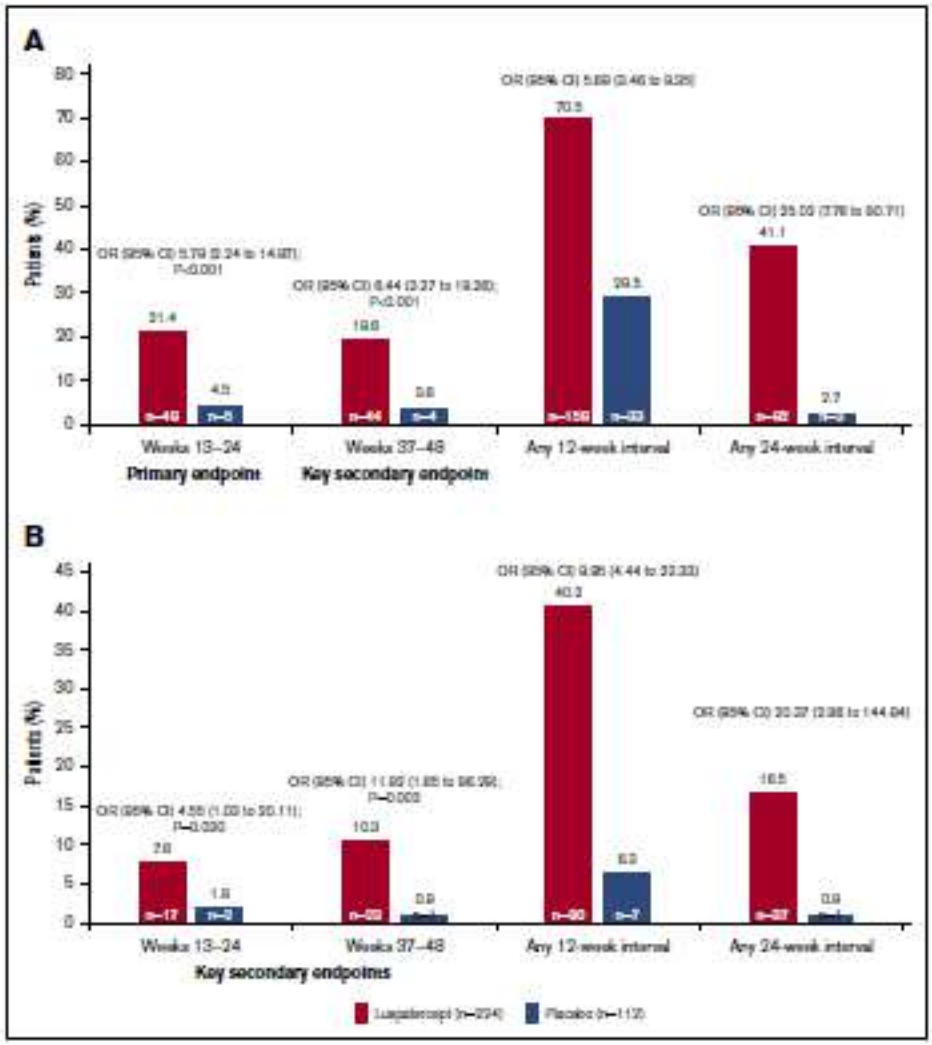
Source: Transcription of (a) Prof. Cappellini's Presentation and (b) Moderated discussion with the panel of International Experts featuring M.D. Cappellini, J. Porter, V. Viprakasit and Y. Aydinok

The KEY SECONDARY END POINTS during the 48 weeks were:
(fist, second and third)

i. a ≥ 33% reduction in RBC transfusion burden from baseline during weeks 37-48 plus a reduction of at least 2 RBC units [2]- First key secondary endpoint (A) achieved in 19.6% of patients (n=44)
ii. a ≥ 50% reduction in RBC transfusion burden from baseline during weeks 13 -24 in 7.6% (n=17) plus a reduction of at least 2 RBC units[3] - Second key secondary endpoint (B)
iii. a ≥ 50% reduction in RBC transfusion burden from baseline during weeks 37-48 in 10.2% (n=23) plus a reduction of at least 2 RBC units over this 12 week period[4] - Third key secondary endpoint (B)

[1] 21.4% (48/224 patients responded vs 4.5% (5/112) on placebo
[2] 19.6% of patients vs 3.6% of placebo
[3] 7.6% of patients vs 1.8% on placebo
[4] 10.3% of patients vs 0.9% on placebo

Figure 7.



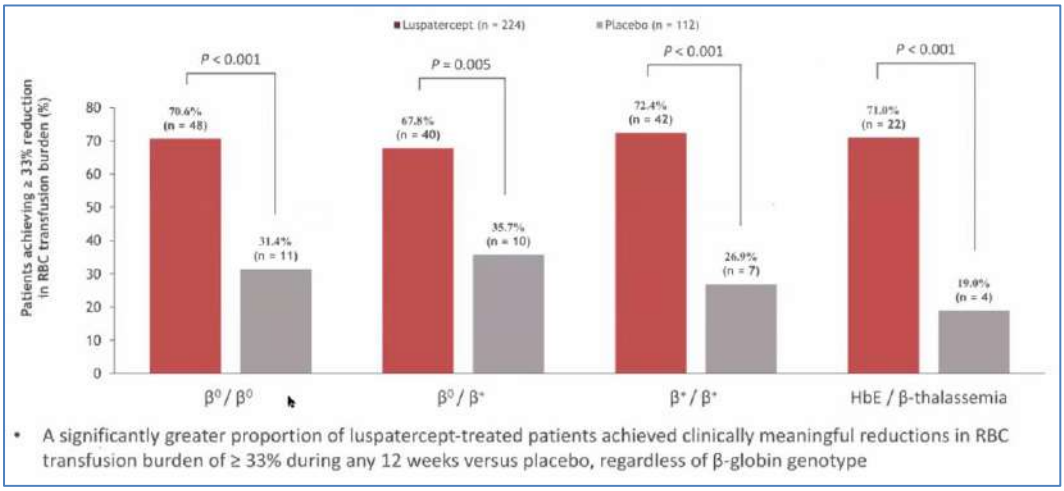
A
Primary (i) and first key secondary end points (ii)

B
Second and third key secondary points end (iii -v)

Source: Blood Advances, Drug Advancse DOI 10.1182/bloodadvances.2020002725

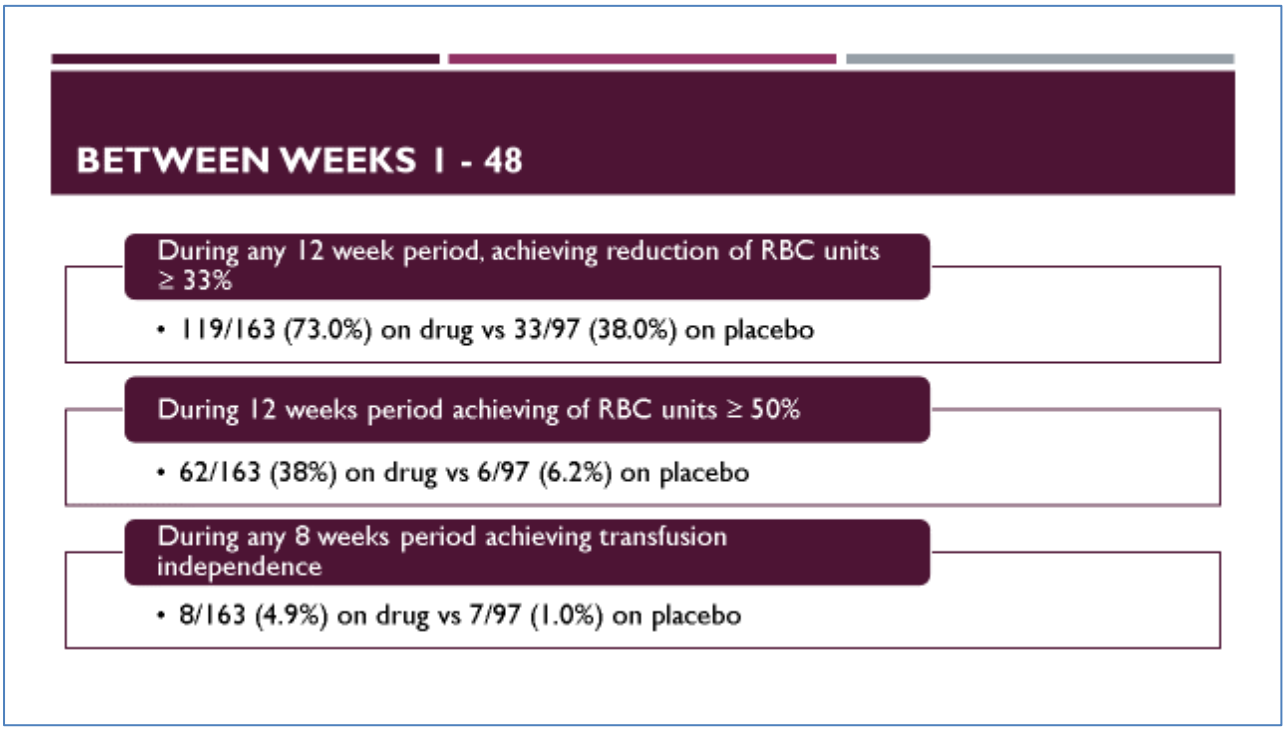
The below figure 8 demonstrates the results across genotypes where ≥33% reduction in RBC Transfusion Burden was achieved during any 12 weeks across genotypes.

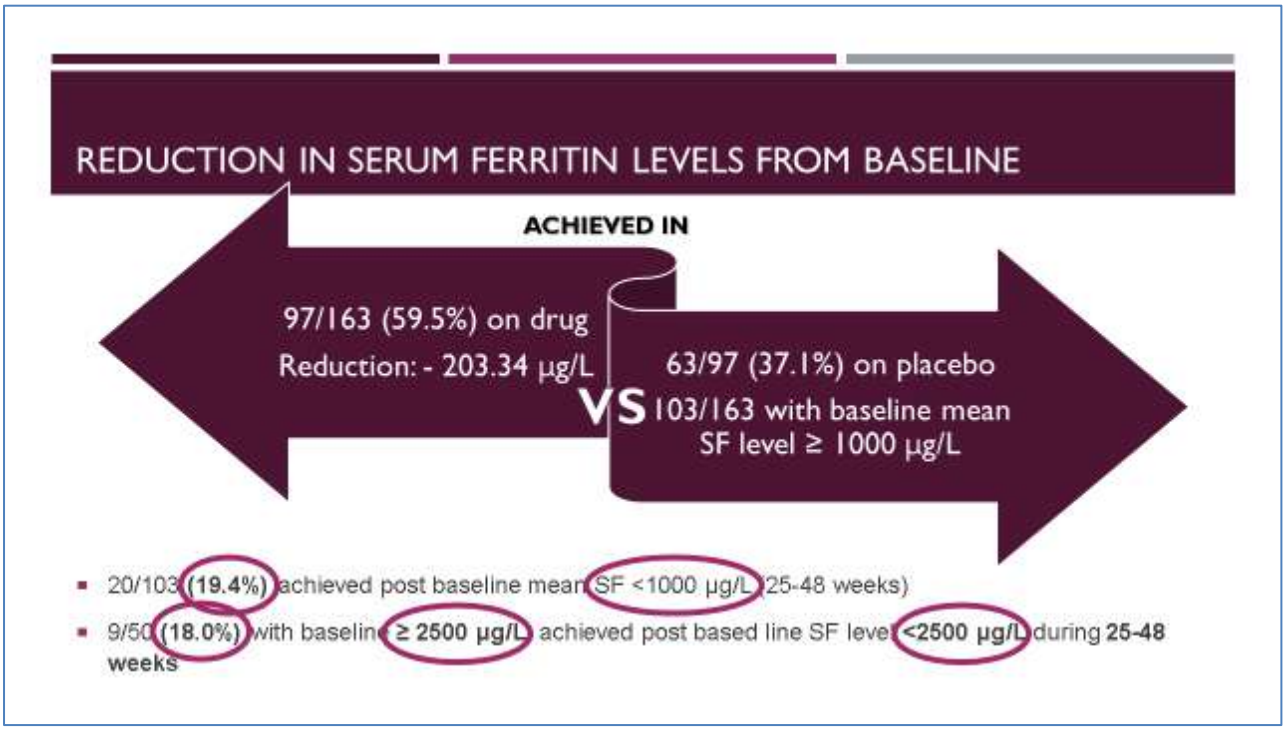
Figure 8.



Source: Transcription of (a) Prof. Cappellini's Presentation and (b) Moderated discussion with the panel of International Experts featuring M.D. Cappellini, J. Porter, V. Viprakasit and Y. Aydinok

In summary the below results were obtained with the use of the drug between 1-48 weeks





Additional endpoints during any 12 weeks or 24 weeks on study (weeks 1-48)

i. A ≥ 50% reduction in RBC transfusion burden from baseline at any 12 week 40.2% (n=90) or 24 week period 16.5% (n=37) 1-48 weeks

ii. During any 8 weeks interval in 8/163 (4.9%) achieved transfusion independence

iii. Medium time to the first response was within the first treatment cycle (12.0 days or 24.5 days) amongst those patients who had reduction of ≥ 33% or ≥ 50% respectively during any 12-week period. 75% of the patients who had at least 33% reductions during any 12-week interval had a response within 86 days (four treatment cycles) and was faster amongst non $\beta^0/\beta^{0.}$ than β^0/β^0 genotypes

iv. The median longest duration of response was 104 days or 98 days amongst patients who had reductions in the transfusion burden from baseline of at least 33% (158 patients) or at least 50% (90 patients) respectively during ANY 12-week interval.

v. After the trial group assignments were unmasked (after 48 weeks) patients randomized to placebo were eligible to cross over to receive luspatercept in an open-label phase. As of July 1st 2019, median treatment duration for patients in the luspatercept and placebo arm (before cross overs) was 119.1 and 74.7 weeks respectively initially randomised to the luspatercept arm. 68.2% were still receiving treatment at the end of 2 years. These patients continued to experience reduction in transfusion burden for 2 years (figure 8).

vi. In addition 80.4% of patients who had at least 33% reduction from baseline during any 12 weeks interval had at least two distinct episodes of response and 51.3% at least four episodes responses (figure 9)

Similarly, 68.9% of the patients who had at least 50% reduction in a 12-week interval had at least two distinct episodes of response and 33% at least four episodes responses (figure 9).

vii. Pre-transfusion haemoglobin levels did not increase over the course of the trial (48 weeks).

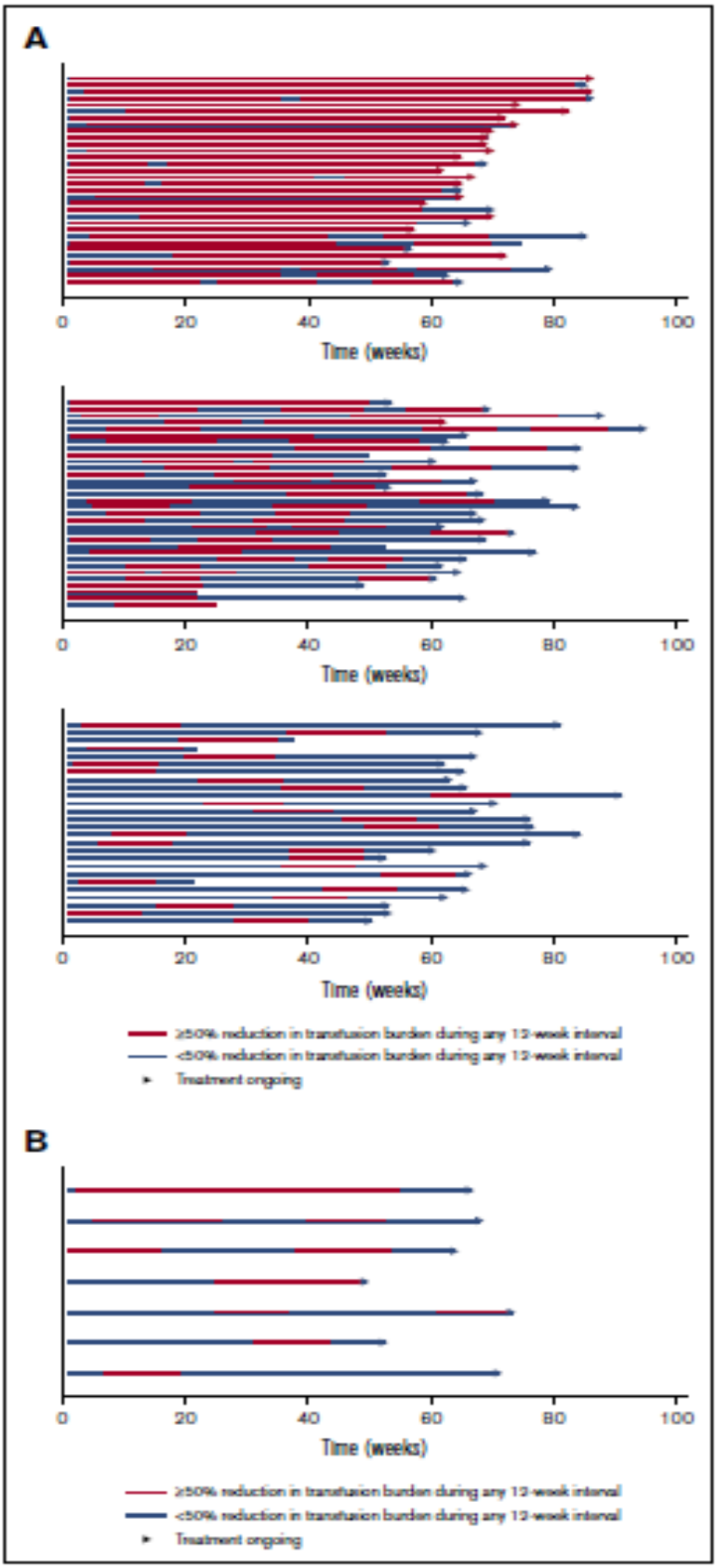
viii. Serum ferritin levels at week 48 were reduced from baseline mean [±SD] change (-248±800 mg per liter).

<u>Serum ferritin (SF): weeks 25-48</u>

- 97/163 (59.5%) luspatercept non-responders achieved a reduction in SF from baseline vs 63/97 (37.1%) patients who received placebo
- For luspatercept non-responders, the mean change in SF from baseline was −203.34 mg/L (−8.1%).
- Of 103 luspatercept non-responders with baseline mean SF ≥1,000 µg/L, 20 (19.4%) achieved post-baseline mean SF level <1,000 µg/L during weeks 25–48.
- Of 50 luspatercept non-responders with baseline mean SF level ≥2,500 µg/L, 9 (18.0%) achieved post-baseline mean SF level <2,500 µg/L during weeks 25–48

No clinically meaningful changes from baseline in liver iron concentration or myocardial iron deposition were observed during the assessment period.

Figure 9.



Source: Blood Advances, Drug Advancse DOI 10.1182/bloodadvances.2020002725

How results translate or mean for the transfusion dependent patient?

- Amongst those who had at least 33% reduction and of at least 50% reduction in transfusion burden it was estimated that 6.55 units and 8.27 units respectively of red cell units from baseline were reduced per patient per 24 week interval

Other subanalysis focused on the assessment of the Quality of Life (QoL) of patients receiving the drug and improvement was clearly demonstrated.

In the below figure 10 treatment related or emergent adverse events (AE) are reported, according to their frequency and severity vs the case of placebo.

Figure 10.

Treatment-Emergent AEs, n (%)	Luspatercept (n = 223)	Placebo (n = 109)
≥ 1 TEAE of any grade	214 (96.0)	101 (92.7)
≥ 1 TEAE of grade ≥ 3	65 (29.1)	17 (15.6)
≥ 1 serious TEAE	34 (15.2)	6 (5.5)
TEAE-related death	0	1 (0.9)*
TEAE-related study drug discontinuation	12 (5.4)	1 (0.9)

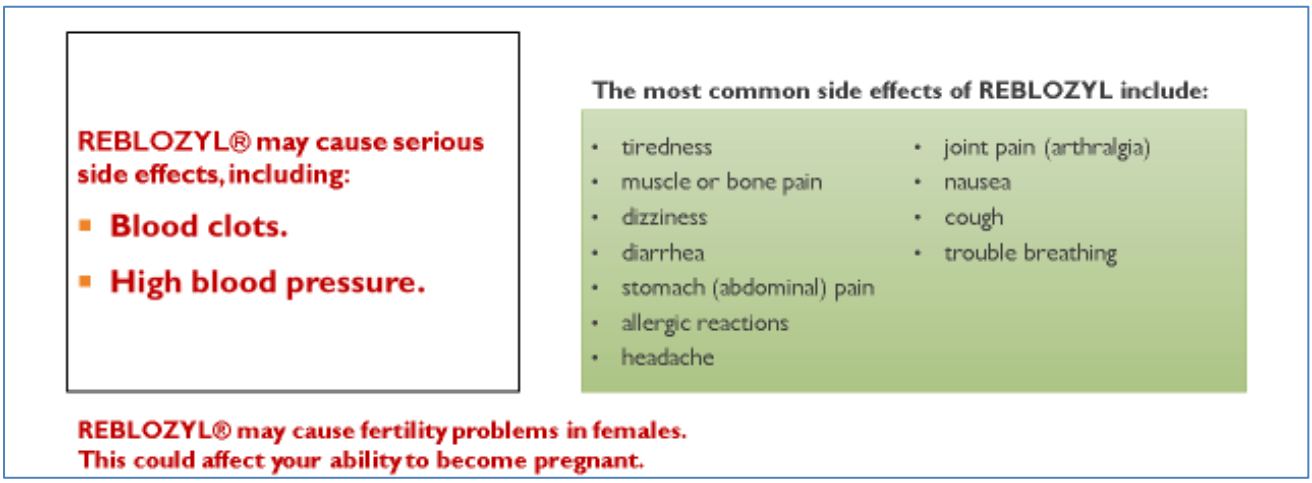
- Among grade ≥ 3 TEAEs, no single organ system or class was predominant
- Only serious TEAE occurring in > 1% of patients in either arm was anemia: luspatercept, n = 3 (1.4%); placebo, n = 0

Source: Transcription of (a) Prof. Cappellini's Presentation and (b) Moderated discussion with the panel of International Experts featuring M.D. Cappellini, J. Porter, V. Viprakasit and Y. Aydinok

Of significance is to note the low numbers of patients who demonstrated serious events and the zero number of deaths.

Below in figure 11, some side effects are reported (more serious in red, most common less serious in green)

Figure 11.



Source: REBLOZYL PATIENT BROCHURE https://www.reblozyl.com/resources-support-bt/

The main adverse events (AE) and the percentage of patients on the drug reporting such events are shown in the below figure 12 (vs percentage of patients on placebo).

Figure 12.

Any Grade TEAE, n (%)	Luspatercept (n = 223)	Placebo (n = 109)
Back pain	61 (27.4)	32 (29.4)
Upper respiratory tract infection	59 (26.5)	36 (33.0)
Headache	58 (26.0)	26 (23.9)
Bone pain	44 (19.7)	9 (8.3)
Arthralgia	43 (19.3)	13 (11.9)
Pyrexia	36 (16.1)	23 (21.1)
Cough	32 (14.3)	12 (11.0)
Fatigue	30 (13.5)	14 (12.8)
Oropharyngeal pain	28 (12.6)	12 (11.0)
Diarrhea	27 (12.1)	11 (10.1)
Dizziness	25 (11.2)	5 (4.6)
Asthenia	22 (9.9)	11 (10.1)
Myalgia	22 (9.9)	11 (10.1)
Pharyngitis	20 (9.0)	13 (11.9)

Source:Transcription of (a) Prof. Cappellini's Presentation and (b) Moderated discussion with the panel of International Experts featuring M.D. Cappellini, J. Porter, V. Viprakasit and Y. Aydinok

DISCUSSION

All these changes described in this summary should be further clarified with long-term observation considering the mechanisms of iron loading, given that unloading from the heart and liver can be slow

Patients with thalassaemia have varying degree of bone marrow suppression caused by the baseline transfusion regime. Therefore long term clinical assessment and evaluation of treatment effects are essential to better reflect the real world data based on real world clinical practice.

A 5-year, open-label extension phase is ongoing to provide longterm efficacy and safety data.

Careful analyses of these findings in the context of iron chelation received is needed. Last, real-world application will help inform how reduction in transfusion burden will be applied by physicians (reduction of number of units per transfusion visit, or delay in transfusion visits) and how it will affect patients' quality of life.

Considering the potential mechanism of action, the use of luspatercept could be explored in other types of anemia that are associated with ineffective erythropoiesis or dyserythropoiesis.

Basic recommendations regarding the use of Reblozyl® (as these are published in TIF's Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition – 2021)

- *Reblozyl*® can be considered for:
    - Patients who require regular red blood cell transfusions.
    - ≥18 years of age

- The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection

- If the pre-dose haemoglobin level is ≥ 115 g/l and is not influenced by recent transfusion, consider delaying dosing of *Reblozyl*® until the level is ≤ 110 g/l

- Before administration of *Reblozyl*® haemoglobin level, and liver function tests including alanine transferase and aspartate transferase levels should be monitored to ensure proper dosing and metabolism of the medication.

- If a TDT patient does not achieve a reduction in red cell transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the *Reblozyl*® dose to 1.25 mg.

- If a patient experienced a response followed by a lack of or lost response to *Reblozyl*®, consider initiating a search for causative factors

- Reblozyl® should be discontinued if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time. However, recent data by Piga et al. has showed that those patients who did not respond to Reblozyl® treatment received clinical benefit from continuing therapy through Week 48 (and beyond, although solid, published results are not yet available). These Reblozyl® non-responders had greater reductions in RBC transfusion units and visits and in serum ferritin levels.
- As thromboembolic events were reported in 8/223 (3.6%) of *Reblozyl*® -treated patients, it is important to monitor any TDT patient receiving *this drug* for signs and symptoms of thromboembolic events and initiate treatment accordingly.

- Hypertension was reported in 10.7% (61/571) of *Reblozyl*®-treated patients. It is therefore recommended that blood pressure be monitored prior to each administration.

- *Reblozyl*® may cause foetal harm. While no data are currently available on its use in pregnant women, all pregnant women should be advised of the potential risk to a foetus.

- Safety and efficacy of *Reblozyl*® in paediatric patients has not yet been established. Its use in paediatric patients in therefore not currently recommended.

For more details regarding Reblozyl®, the treating doctor can refer to the EMA(European Medicines Agency - https://www.ema.europa.eu/en) and/or the FDA (Food and Drug Administration - https://www.fda.gov) summaries of product characteristics.

IMPORTANT INFORMATION FROM THE EUROPEAN MEDICINES AGENCY (EMA)

Indications for Discontinuation – When is the drug discontinued

The most serious causes include the following:

1. Thrombosis / Thromboembolism: In adult patients with beta thalassaemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) Reblozyl®-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Thromboprophylaxis in patients with beta thalassemia at increased risk of TEE should hence be considered in patients receiving Reblozyl® who should be monitored for signs and symptoms of thromboembolic events for their prompt treatment.

2. Hypertension: Hypertension was reported in 10.7% (61/571) of Reblozyl®-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with beta thalassaemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) > 130mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) > 80 mm Hg. Blood pressure should thus be monitored prior to each administration and new-onset hypertension or exacerbation of pre-existing hypertension should be promptly monitored using anti-hypertensive agents.

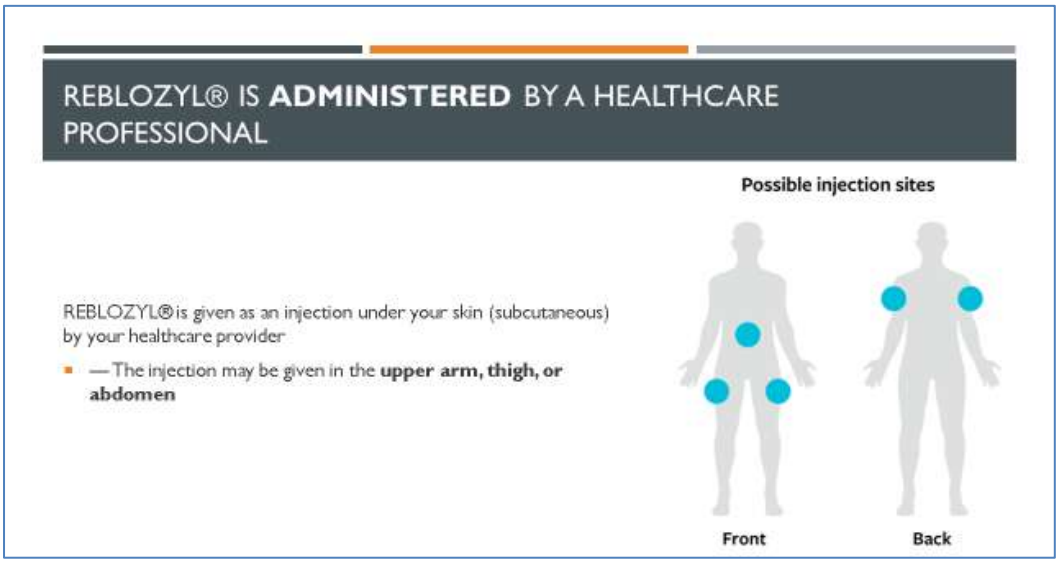
3. Embryo-Fetal toxicity: Based on findings from animal reproductive studies, Reblozyl® may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aapt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.25 mg/kg.

However, the treating physician should exert very close and regular monitoring of his/her patients taking the drug and very importantly the patients themselves or their parents (in case the patients are children), should be alert and cautions of any problems mentioned or observed during the treatment.

Administration of the drug

Any new drug needs careful, close and regular monitoring post authorization to collect Real World Data. These will help better selection of patients who will benefit the most with the use of the drug while at the same time promptly prevent progression of any known or still unknown or even evidence related sides effects.

Figure 13.



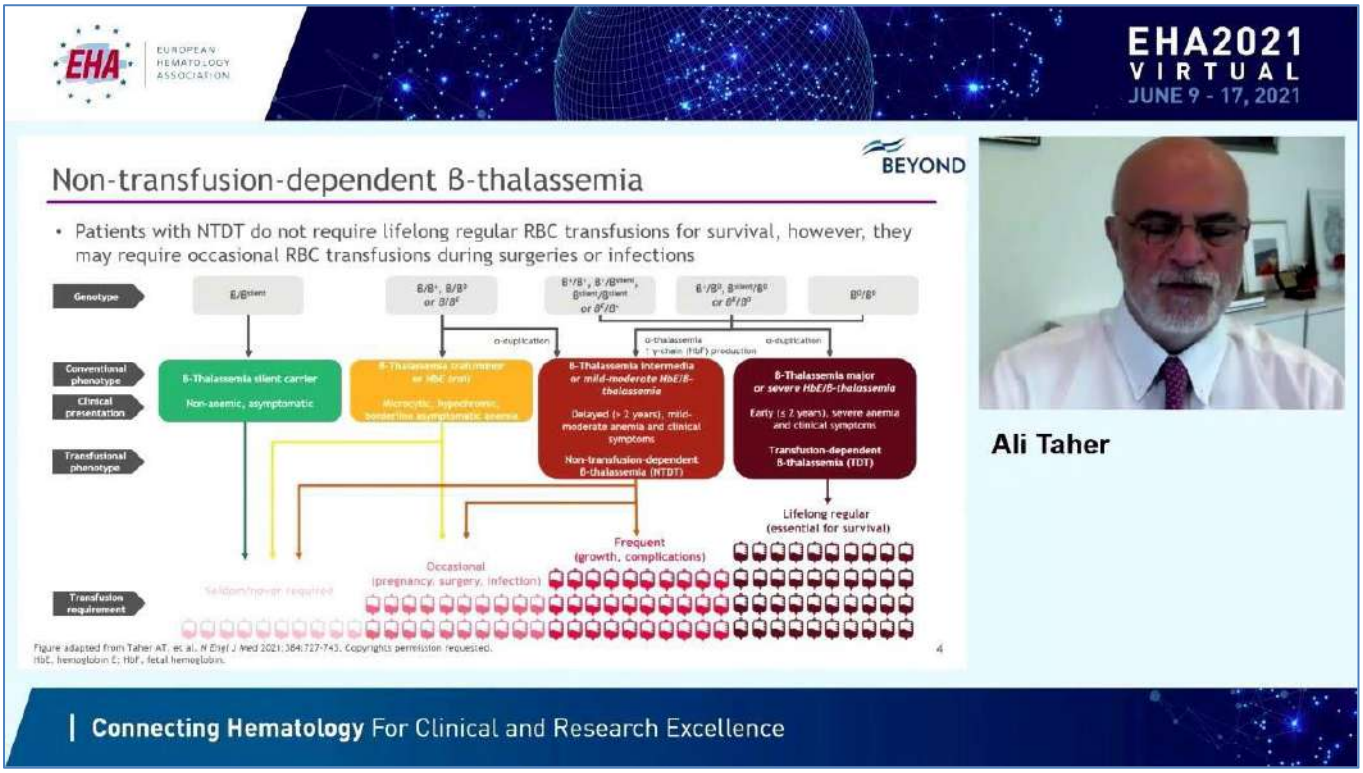
Source: REBLOZYL PATIENT BROCHURE https://www.reblozyl.com/resources-support-bt/

Recommended Dose & Administration Methodology

i. The recommended starting dose is 1mg/kg, once every 3 weeks, by subcutaneous injection;
ii. The Haemoglobin level of the patient is reviewed before each administration;
iii. There are two preparations:
- Each vial containing 25mg powder to be reconstituted in 0.68ml of sterile water
- Each vial containing 75mg powder to be reconstituted in 1.6ml of sterile water
- After reconstitution the liquid is, clear and colourless to slightly yellow
- The preparation can be stored at room temperature for up to 8 hours or refrigerated up to 24 hoursand must NOT under ANY circumstances be frozen.

THE BEYOND TRIAL FOR NON TRANSFUSION DEPENDENT THALASSAEMIA (NTDT)

Figure 14.



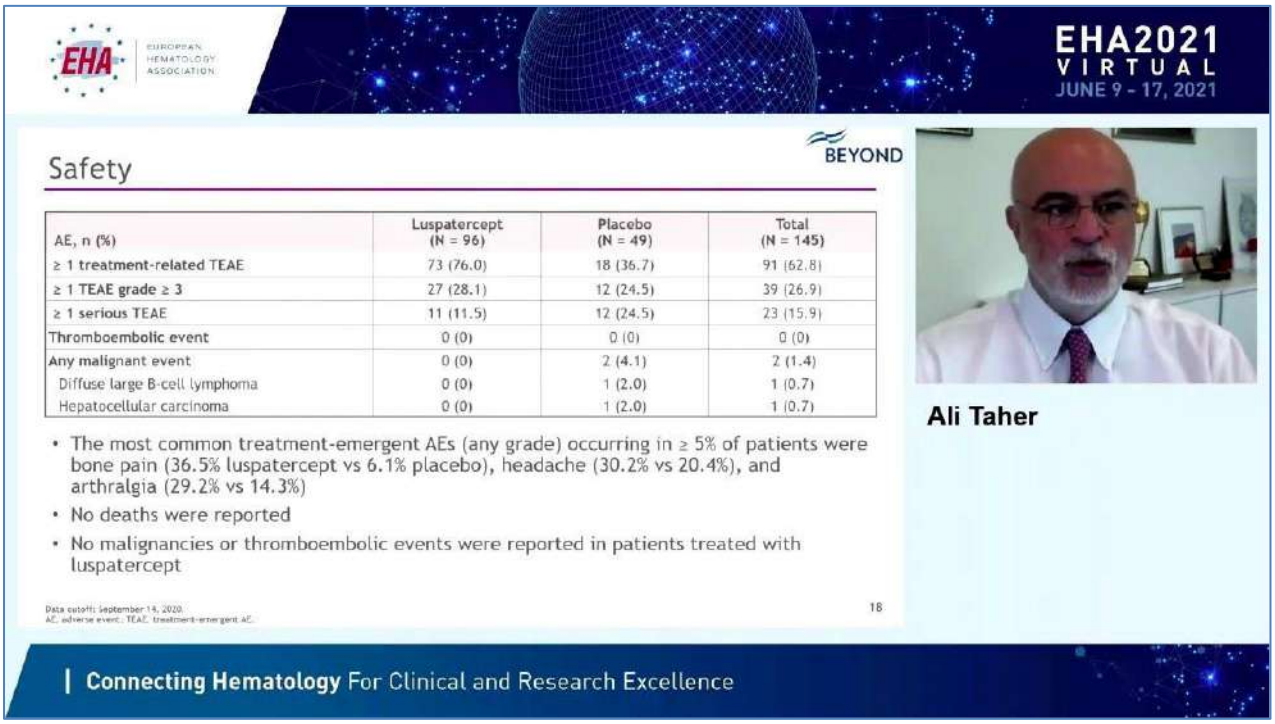
Source: 26th EHA Annual Congress, held this year virtually on 09 - 17 June 2021, TIF Special Report

Data from the BEYOND trial were presented at EHA2021[5]. BEYOND is a Phase 2, randomized, double-blind, placebo-controlled multi-center study to determine the efficacy and safety of Reblozyl in non-transfusion dependent (NTD) beta thalassemia.

- 145 eligible patients over 18 years of age with beta thalassemia or hemoglobin (Hb) E beta thalassemia and who received ≤5 red blood cell (RBC) units in the 24 weeks prior to the trial with mean baseline Hb ≤10.0 g/dL participated.
- The primary endpoint was achievement of ≥1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval, sustained without of RBC transfusions.
- 77.1% of participants achieved an increase in haemoglobin compared to 0% patients on placebo. Of these, 72.7% of patients had a mean baseline Hb of <8.5 g/dL.
- 89.6% of patients treated with Reblozyl remained transfusion free for at least 24 weeks vs. 67.3% of patients in the placebo arm.

[5] Sources:
EHA2021: Presidential Symposium: The BEYOND Study: Results of a Phase 2, double-blind, randomized, placebo-controlled multi-center study of luspatercept in adult patients with non-transfusion dependent beta-thalassemia
https://news.bms.com/news/corporate-financial/2021/Bristol-Myers-Squibb-and-Acceleron-Present-First-Results-from-Phase-2-BEYOND-Study-of-Reblozylluspatercept-aamt-in-Adults-with-Non-Transfusion-DependentNTDBeta-Thalassemia/default.aspx

Figure 15.



26th EHA Annual Congress, held this year virtually on 09 - 17 June 2021, TIF Special Report

Patients primary endpoint of mean haemoglobin level increase of ≥ 1.0g/dl from baseline over a continuous 12-week interval during weeks 13-24 in the absence of RBC transfusion:

Improved quality of life as measured by the NTDT-PRO T/Q domain score was demonstrated and this was correlated with increase in haemoglobin levels.

After the drug's authorization for NTD thalassaemia, recommendations and further guidance will be provided by health experts.

REFERENCES

1. The use of luspatercept for thalassemia in adults, Maria Domenica Cappellini, Ali T. Taher,Blood Adv (12 Jan 2021) Vol 5, No1 (326–333)

2. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia, The New England Journal of Medicine, March 26, 2020; 382:1219-1231

3. Prescribing Information and Patient Information for Reblozyl, Summaries of product characteristics https://www.ema.europa.eu/eu, https://www.fda.gov

4. The Centre of Disease Control and Prevention https://www.cdc.gov/ncbddd/thalassemia/index.html

GLOSSSARY

Anemia: Low red blood cell count
Beta globin: A protein building block of hemoglobin
Blood pressure: The force of circulating blood on the walls of blood vessels
Bone marrow: The soft interior of the bones where new blood cells are created
Chelating agent: A chemical compound used to remove toxic metals from the body
Erythroid cell: An immature red blood cell
Erythroid maturation agent: Treatment that helps young cells become mature cells
Erythropoiesis: The formation of red blood cells in blood-forming tissue within the bone marrow
Erythropoiesis-stimulating agent: A manufactured growth hormone that helps the body produce more immature red blood cells
Hemoglobin: Oxygen-carrying protein found in red blood cells
Hydroxyurea: A type of medicine used to treat certain cancers
Immunosuppressant: An agent that decreases the body's immune response
Ineffective erythropoiesis: The inability of oxygencarrying red blood cells to leave the bone marrow
Ischemic stroke: The most common type of stroke, caused by a blood clot that blocks a blood vessel in the brain
Median: A statistics term. The middle of a range of numbers
Mutation: An abnormal change within a gene
Placebo: An inactive substance that looks the same as, and is given the same way as, an active drug or treatment being tested
Red blood cells (RBCs): Blood cells that carry oxygen from the lungs to all cells in the body
Red blood cell transfusion: A process that adds red blood cells into the bloodstream
Subcutaneous: Under the skin
Thromboembolic event: Formation of a clot in a vein or artery that breaks loose and is carried by the blood to block a blood vessel
Thrombosis: Formation of a blood clot
Uric acid: A chemical created when the body breaks down certain substances made by the body and found in some foods and drinks and is removed from the body by the kidneys. Too much uric acid in your body can cause you to become sick