Duration of response to luspatercept in patients requiring red blood cell transfusions with myelofibrosis – updated data from the phase 2 ACE-536-MF-001 study

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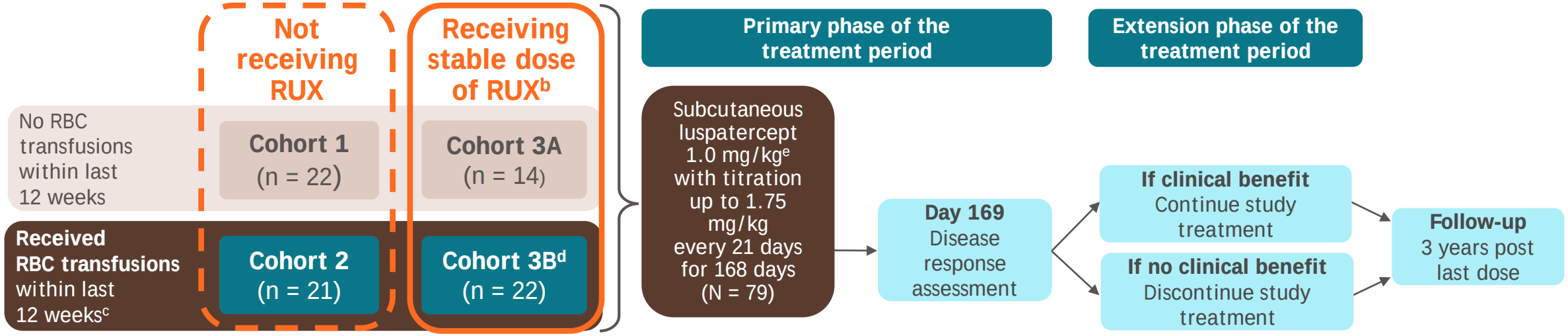
ACE-536-MF-001 study design

- This study reports the results of the ongoing open-label, phase 2 ACE-536-MF-001 trial evaluating luspatercept in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions (NCT03194542)

Figure 1. ACE-536-MF-001 study design[a]



- 79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)
- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. [a]Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; [b]A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; [c]6–12 RBC units/84 days prior to treatment; or 4–12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; [d]Including 3 subjects enrolled in the expansion cohort; [e]The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.

Baseline characteristics

Table 1. Baseline characteristics

Characteristic	No RBC transfusions[a]		Receiving RBC transfusions[a]		Overall (N = 79)
	Not receiving RUX[b]	Receiving RUX[b]	Not receiving RUX[b]	Receiving RUX[b]	
	Cohort 1 (n = 22)	Cohort 3A (n = 14)	Cohort 2 (n = 21)	Cohort 3B (n = 22)	
Age, median (range), years	69.0 (50-89)	64.5 (51-81)	75.0 (59-88)	71.0 (59-83)	71.0 (50-89)
Male, n (%)	13 (59.1)	7 (50.0)	25 (71.4)	11 (50.0)	46 (58.2)
Most recent pathology, n (%)					
Primary MF	15 (68.2)	7 (50.0)	13 (61.9)	10 (45.5)	45 (57.0)
Post-ET MF	7 (31.8)	3 (21.4)	6 (28.6)	7 (31.8)	23 (29.1)
Post-PV MF	0	4 (28.6)	2 (9.5)	5 (22.7)	11 (13.9)
Time since initial MF diagnosis					
≤ 2 years, n (%)	10 (45.5)	2 (14.3)	6 (28.6)	2 (9.1)	20 (25.3)
> 2 years, n (%)	12 (54.5)	12 (85.7)	15 (71.4)	20 (90.9)	59 (74.7)
DIPSS risk category,[c] n (%)					
Intermediate-1	1 (4.5)	4 (28.6)	1 (4.8)	1 (4.5)	7 (8.9)
Intermediate-2	18 (81.8)	9 (64.3)	15 (71.4)	21 (95.5)	63 (79.7)
High	2 (9.1)	1 (7.1)	5 (23.8)	0	8 (10.1)
Unknown	1 (4.5)	0	0	0	1 (1.3)
Baseline Hb level, median (range), g/dL	8.8 (6.7-10.0)	8.6 (6.7-9.1)	NA	NA	NA
Screening pretransfusion Hb level, median (range), g/dL	NA	NA	7.4 (6.1-9.1)	8.1 (6.4-9.2)	NA
Baseline RBC transfusion burden, median (range), U/28 days	NA[d]	NA	2.7 (1-5)	2.7 (2-4)	2.7 (1-5)
8 cycles of luspatercept (range 1-39),[e] weeks	NA	NA	24 (31)	23 (39)	NA

Data cutoff: March 29, 2020.
[a]In the 12 weeks prior to treatment; [b]A stable daily dose of RUX for ≤ 16 weeks at enrollment; [c]DIPSS category unknown for 1 subject; [d]1 subjects in Cohort 1 received RBC transfusion (1 U RBC) prior to luspatercept administration; [e]Applicable only to subjects in Cohorts 2 and 3B.
DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; NA, not applicable; Post-ET, post-essential thrombocythemia; Post-PV, post–polycythemia vera; U, unit.

Response rates among subjects receiving RBC transfusions

Table 2. Response rates

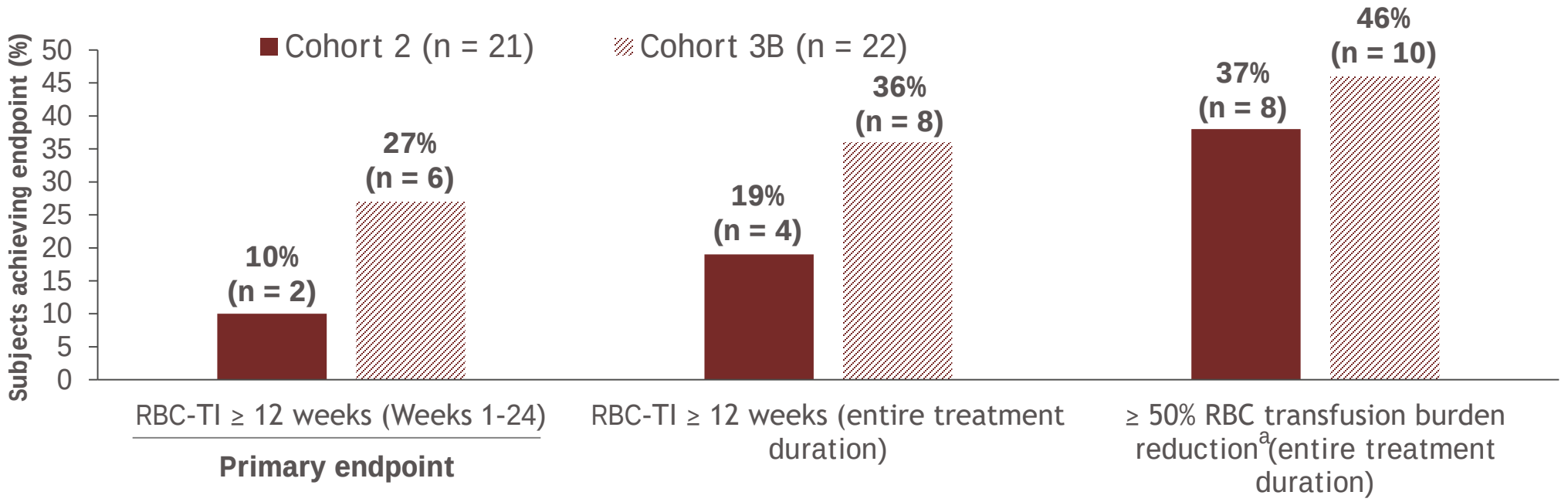
Response	Cohort 2 (n = 21)	Cohort 3B (n = 22)
RBC-TI ≥ 12 weeks (Weeks 1-24), n (%)	2 (10)	6 (27)
Time to first onset of RBC-TI ≥ 12 weeks, median (range), days	1.5 (1–2)	37 (1–71)
Duration of RBC-TI ≥ 12 weeks, median (range), weeks	49 (16–82)	42 (12–111)
RBC-TI ≥ 12 weeks (entire treatment period), n (%)	4 (19)	8 (36)
Cumulative duration of all RBC-TI ≥ 12 weeks episodes, median (range), weeks	59 (24–82)	55 (12–116)
Number of responders[a] by baseline transfusion burden, n/N (%)		
4 – < 6 U/12 weeks	0/1 (0)	0/1 (0)
6 – < 9 U/12 weeks	1/10 (10)	5/15 (33)
9 – 12 U/12 weeks	1/7 (14)	1/6 (17)
> 12 U/12 weeks	0/3 (0)	0/0 (0)
Overall	2/21 (10)	6/22 (27)

- Among the subjects who reached 24 weeks of treatment, 4 of 15 (27%) and 8 of 14 (57%) in Cohorts 2 and 3B achieved clinical benefit[b] and therefore continued to receive luspatercept after 24 weeks

Data cutoff: March 29, 2020.[a]Response defined as RBC-TI ≥ 12 weeks (Weeks 1-24); [b]Clinical benefit defined as achievement of RBC-TI ≥ 12 weeks.
RBC-TI, RBC transfusion independence.

Achievement of RBC-TI ≥ 12 weeks, ≥ 50% transfusion burden reduction, and multiple response episodes

Figure 2. Rates of RBC-TI and ≥ 50% transfusion burden reduction ≥ 12 weeks



Achievement of multiple episodes of response

- Of the RBC-TI ≥ 12-week responders in both Cohorts 2 and 3B, 25% experienced two separate episodes of RBC-TI ≥ 12 weeks
- Of the subjects who achieved ≥ 50% reduction in RBC transfusion burden over any 12 weeks, 3 subjects in Cohort 2 (38%) and 2 subjects in Cohort 3B (20%) experienced two separate ≥ 12-week response episodes
  - 1 subject (13%) in Cohort 2 experienced three separate episodes of RBC-TI ≥ 12 weeks

[a]Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.

Safety

Table 3. Safety

Safety assessment	All subjects (N = 79)
≥ 1 treatment-related AE (any grade), n (%)	31 (39)
≥ 1 treatment-related grade 3–4 AE, n (%)	5 (6)
Treatment-related AEs leading to death, n (%)	0
Treatment-related AE leading to treatment discontinuation,[a] n (%)	8 (10)

- TEAEs (any grade) occurring in ≥ 15% of subjects were diarrhea (23%), hypertension (19%), thrombocytopenia (19%), dyspnea (17%), fatigue (17%), and pyrexia (17%)
- Treatment-related AEs (any grade) occurring in ≥ 5% of subjects were hypertension (13%), bone pain (9%), and diarrhea (5%)
- 5 subjects had grade 3-4 treatment-related AEs, which were diarrhea (n = 2), dehydration (n = 1), and hypertension (n = 3)
- 2 subjects had treatment-related serious AEs, which were diarrhea and urinary tract infection

[a]Treatment-related AEs leading to discontinuation: anemia, splenomegaly, fatigue, general physical health deterioration, sepsis, urinary tract infection, diverticular perforation, and hemorrhage.
AE, adverse event; TEAE, treatment-emergent AE.

Summary

- This updated analysis suggests durable activity of luspatercept in RBC transfusion dependent subjects with MF-associated anemia
- In addition, a quarter of subjects receiving transfusions achieved more than one ≥ 12-week episode of RBC-TI response with luspatercept
- The incidence of grade 3–4 treatment-related AEs with luspatercept was low
- Those data warrant further investigation in a controlled study of luspatercept as a potential treatment for patients with MF-associated anemia

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