ABSTRACT 557

A Phase 2 Study of Luspatercept in Patients With Myelofibrosis-Associated Anemia

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INTRODUCTION

- Approximately 40% of patients with myelofibrosis (MF) have anemia (hemoglobin [Hb] < 10 g/dL) at diagnosis; the majority will develop chronic anemia throughout the course of their disease[1]
- Around 25% of patients are dependent on red blood cell (RBC) transfusions to manage their anemia at time of MF diagnosis, with transfusion dependency increasing over time[1]
- JAK inhibitors have become standard treatment for MF, but have the added effect of worsening anemia in around 25% of patients[2,3]

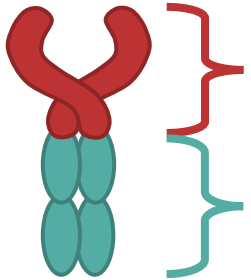
Hb, hemoglobin; MF, myelofibrosis; RBC, red blood cell.

1. Tefferi A, et al. Mayo Clin Proc. 2012;87:25-33.
2. Harrison CN, et al. Leukemia. 2016;30:1701-1707.
3. Mesa RA, et al. J Clin Oncol. 2013;31:1285-1292.

INTRODUCTION (cont.)

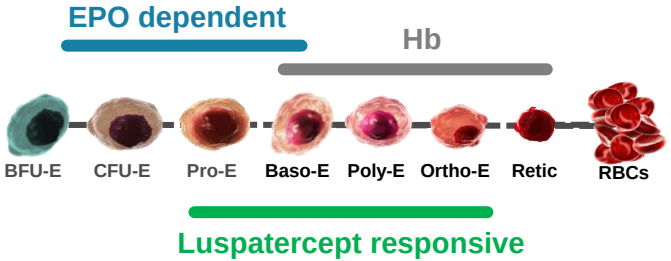
- Luspatercept is a first-in-class erythroid maturation agent that binds several TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[1]
- Luspatercept is approved by the US FDA for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions[2]
- The aim of this ongoing, open-label phase 2 trial is to evaluate the efficacy and safety of luspatercept in patients with MF (NCT03194542)

Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein



Modified extracellular domain of ActRIIB

Human IgG1 Fc domain



ActRIIB, human activin receptor type IIB; Baso-E, basophilic erythroblast; BFU-E, burst-forming unit–erythroid; CFU-E, colony-forming unit–erythroid; EPO, erythropoietin; IgG1 Fc, immunoglobulin G1 fragment crystallizable; Ortho-E, orthochromatic erythroblast; Poly-E, polychromatophilic erythroblast; Pro-E, proerythroblast; retic, reticulocyte; TGF-β, transforming growth factor beta; US FDA, United States Food and Drug Administration.

1. Suragani RN, et al. Nat Med. 2014;20:408-414.
2. Reblozyl [package insert]. Summit, NJ: Celgene Corporation; 2019.

PATIENT POPULATION

Key Eligibility Criteria

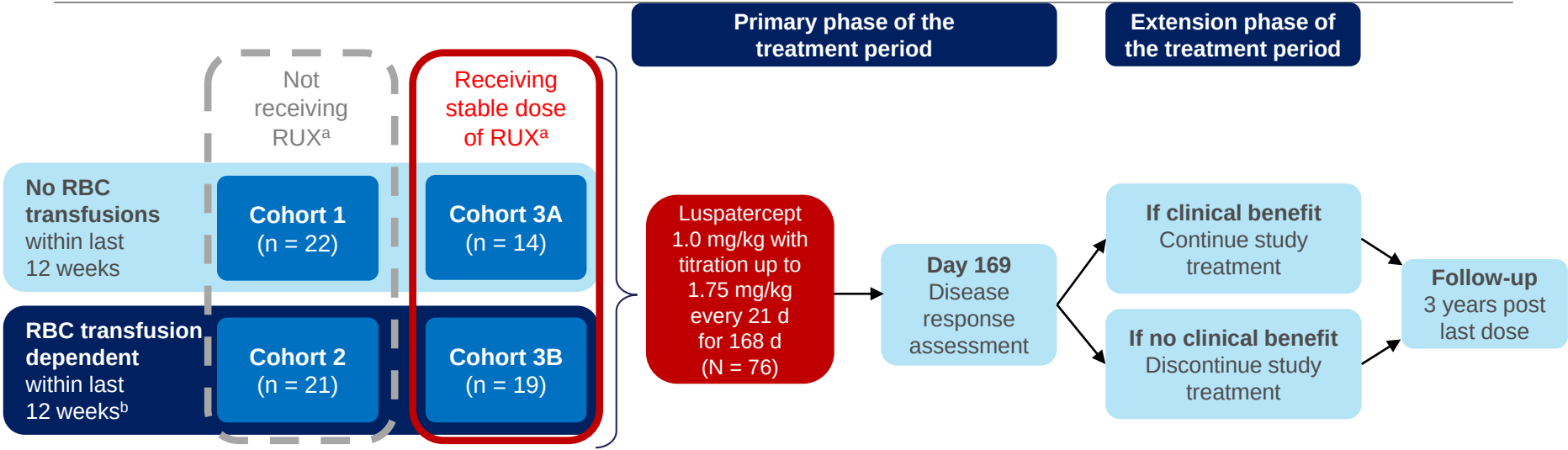
- Adults with primary or post-essential thrombocythemia (ET) / post-polycythemia vera (PV) MF
- Anemia (RBC transfusion-dependent or anemic without requiring RBC transfusions)
- Blood myeloblasts < 5%
- Not receiving hydroxyurea, ESAs, lenalidomide, pomalidomide, thalidomide, or androgenic steroids in the 16 weeks prior to enrollment

Data Cut Off

- 76 patients had been enrolled by the data cutoff for this preliminary analysis (Aug 5, 2019)

ESAs, erythropoiesis-stimulating agents; post-ET, post-essential thrombocythemia; post-PV, post-polycythemia vera.

STUDY DESIGN



- **No RBC transfusions (Cohorts 1 & 3A)**
  - No RBC transfusions within 12 weeks before enrollment
  - Hb levels ≤ 9.5 g/dL (recorded on 3 separate occasions, with ≥ 14 d between each measurement)
- **RBC transfusions (Cohorts 2 & 3B)**
  - RBC transfusion dependent (2–4 RBC U/28 d within 12 weeks before enrollment)
  - No transfusion-free interval > 6 weeks

[a] A stable daily dose of RUX for at least 16 weeks at enrollment. [b] 2–4 RBC U/28 d transfused within last 12 weeks.
d, day; RUX, ruxolitinib; U, unit.

STUDY ENDPOINTS

Primary Endpoint[a]

Patients not receiving RBC transfusions (**Cohorts 1 and 3A**):

- Hb increase ≥ 1.5 g/dL from baseline over any consecutive 12-week period (at each assessment) without an RBC transfusion

Patients receiving RBC transfusions (**Cohorts 2 and 3B**):

- RBC transfusion free for ≥ 12 consecutive weeks

Select Secondary Endpoints[a]

All patients:

- Incidence of treatment-emergent adverse events (TEAEs)

Patients not receiving RBC transfusions (**Cohorts 1 and 3A**):

- Mean Hb increase ≥ 1.5 g/dL from baseline for ≥ 12 consecutive weeks

Patients receiving RBC transfusions (**Cohorts 2 and 3B**):

- ≥ 50% decrease in RBC transfusions from baseline for ≥ 12 consecutive weeks (minimum 4 RBC U decrease)
- Duration of RBC transfusion-free period (in RBC transfusion free ≥ 12 consecutive weeks responders)

[a] For efficacy endpoints: responses occurring within the first 24 weeks of study entry. The efficacy analysis was performed on the ITT population.
ITT, intent to treat; TEAE, treatment-emergent adverse event.

BASELINE PATIENT CHARACTERISTICS

Characteristic	No RBC Transfusions[a]		RBC Transfusion Dependent[a]		Overall (N = 76)
	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 = 19)	
Age, median (range), years	**69.0 (50–89)**	**64.5 (51–81)**	**75.0 (59–88)**	**72.0 (59–83)**	**71.0 (50–89)**
Male, n (%)	**13 (59)**	**7 (50)**	**15 (71)**	**9 (47)**	**44 (58)**
Most recent pathology, n (%)					
Primary MF	15 (68)	7 (50)	13 (62)	8 (42)	43 (57)
Post-ET MF	7 (32)	3 (21)	6 (29)	6 (32)	22 (29)
Post-PV MF	0	4 (29)	2 (10)	5 (26)	11 (15)
Time since initial MF diagnosis					
≤ 2 years, n (%)	10 (46)	2 (14)	6 (29)	1 (5)	19 (25)
> 2 years, n (%)	12 (55)	12 (86)	15 (71)	18 (95)	57 (75)
DIPSS risk category[c]					
Intermediate-1	1 (5)	4 (29)	1 (5)	1 (5)	7 (9)
Intermediate-2	18 (82)	9 (64)	15 (71)	18 (95)	60 (79)
High	2 (9)	1 (7)	5 (24)	0	8 (11)
Baseline Hb level, median (range), g/dL	**8.8 (6.7–10.0)**	**8.6 (6.7–9.1)**	**N/A**	**N/A**	**N/A**
Baseline RBC transfusion burden, median (range), U/28 d	**N/A**	**N/A**	**2.7 (1–5)**	**2.3 (2–4)**	**N/A**

[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 patient.
DIPSS, Dynamic International Prognostic Scoring System; N/A, not applicable.

Preliminary findings – data cutoff: Aug 5, 2019

BASELINE PATIENT CHARACTERISTICS (cont.)

Characteristic	No RBC Transfusions[a]		RBC Transfusion Dependent[a]		Overall (N = 76)
	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 = 19)	
Baseline serum erythropoietin, median (range), U/L	**52 (7–1,997)**	**158 (30–2,395)**	**140 (16–1,594)**	**87 (6–915)**	**97 (6–2,395)**
Platelet count, median (range), × 10^9/L	**167 (33–434)**	**260 (54–667)**	**128 (38–880)**	**118 (75–335)**	**150 (33–880)**
Prior therapy received, n (%)[c]					
ESAs	6 (27)	2 (14)	6 (29)	2 (11)	16 (21)
Danazol	3 (14)	0	7 (33)	0	10 (13)
Thalidomide	0	0	1 (5)	0	1 (1)
Lenalidomide	0	0	2 (10)	0	2 (3)
RUX[d]	2 (9)	N/A	6 (29)	N/A	N/A
RUX daily dose received, median (range), mg/d[e]	**N/A**	**20 (5–50)**	**N/A**	**20 (5–40)**	**N/A**
Duration of prior RUX therapy, median (range), weeks	N/A	57 (22–315)	N/A	69 (30–411)	N/A

[a] In the 12 weeks prior to treatment. [b] A stable daily dose of RUX for ≤ 16 weeks at enrollment. [c] Not received within the 16 weeks prior to enrollment. [d] The patients who received prior RUX in Cohorts 1 and 2 did not receive RUX within the 16 weeks prior to enrollment. [e] Within the 16 weeks prior to enrollment.

Preliminary findings – data cutoff: Aug 5, 2019

TREATMENT EXPOSURE

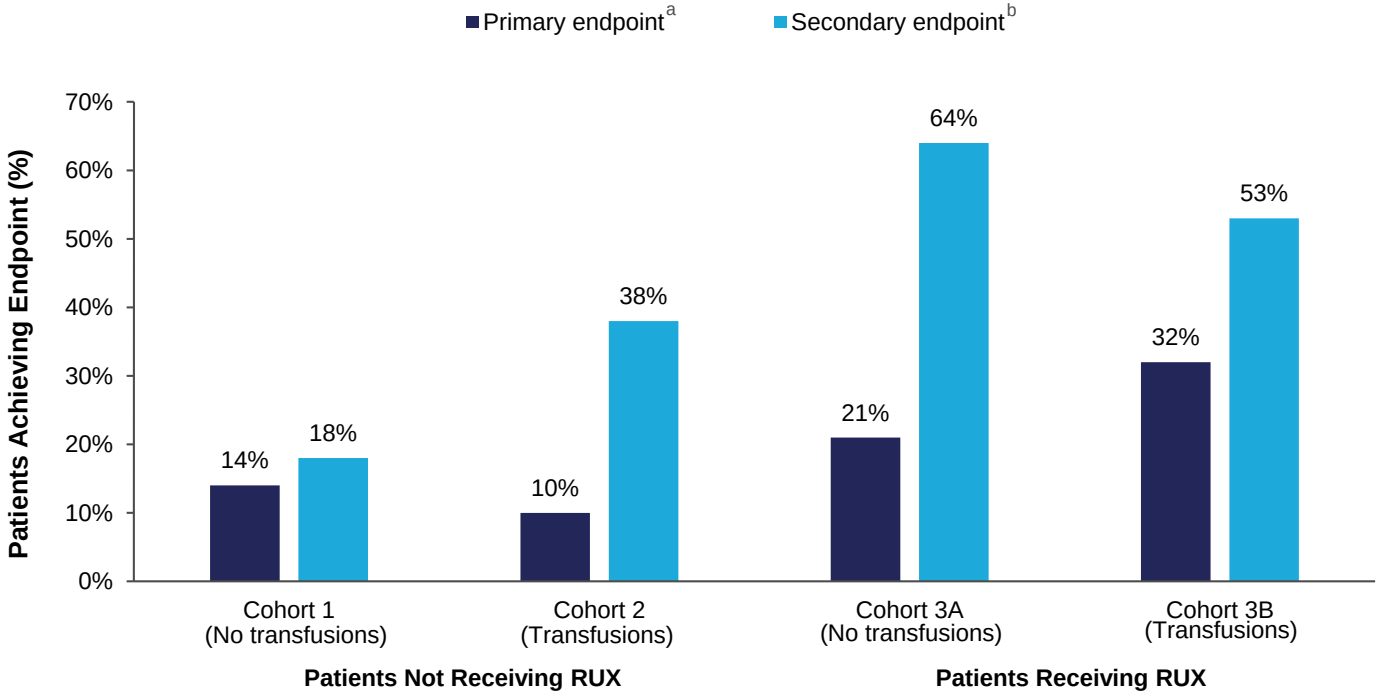
Characteristic	No RBC Transfusions[a]		RBC Transfusion Dependent[a]		Overall (N = 76)
	Not Receiving RUX[b]	Receiving RUX[b]	Not Receiving RUX[b]	Receiving RUX[b]	
	Cohort 1 (n = 22)	Cohort 3A (n = 14)	Cohort 2 (n = 21)	Cohort 3B (n = 19)	
Treatment duration, median (range), weeks	**24.0 (2.1–60.1)**	**24.2 (10.7–85.6)**	**24.0 (11.4–53.7)**	**24.0 (3.0–82.0)**	**24.0 (2.1–85.6)**
Number of doses received, median (range)	**8 (1–19)**	**8 (3–26)**	**8 (4–18)**	**8 (1–28)**	**8 (1–28)**
Dose escalations, n (%)					
1.33 mg/kg	19 (86)	11 (79)	21 (100)	14 (74)	65 (86)
1.75 mg/kg	14 (64)	9 (64)	17 (81)	10 (53)	50 (66)
On treatment at time of data cutoff, n (%)	**7 (32)**	**3 (21)**	**3 (14)**	**6 (32)**	**19 (25)**
RUX daily dose received, median (range), mg/d[c]	**N/A**	**20 (5–50)**	**N/A**	**20 (5–40)**	**N/A**

- RUX daily dose remained stable throughout the 24-week treatment period in both Cohorts 3A and 3B

[a] In the 12 weeks prior to treatment. [b] A stable daily dose of RUX for ≤ 16 weeks at enrollment. [c] Within the 16 weeks prior to enrollment.

Preliminary findings – data cutoff: Aug 5, 2019

ACHIEVEMENT OF THE PRIMARY AND SECONDARY EFFICACY ENDPOINTS



- The median duration of RBC transfusion independence ≥ 12 weeks was 32 and 39 weeks for Cohorts 2 and 3B

[a] For patients not receiving RBC transfusions: Hb increase ≥ 1.5 g/L at every assessment from baseline for ≥ 12 consecutive weeks, within the first 24 weeks on study. For patients receiving RBC transfusions: RBC transfusion free for ≥ 12 consecutive weeks, within the first 24 weeks on study.

[b] For patients not receiving RBC transfusions: mean Hb increase ≥ 1.5 g/dL from baseline for ≥ 12 consecutive weeks. For patients receiving RBC transfusions: ≥ 50% reduction in RBC transfusion burden from baseline.

SAFETY

Patient Safety Assessment	No RBC Transfusions[a]		RBC Transfusion Dependent[a]	
	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 = 19)
≥ 1 treatment-related TEAE (any grade), n (%)	14 (64)	7 (50)	5 (24)	4 (21)
≥ 1 treatment-related grade 3–4 TEAE, n (%)	0	2 (14)	0	1 (5)
≥ 1 treatment-related SAE, n (%)[c]	1 (5)	0	0	1 (5)
TEAE leading to death, n (%)[d]	1 (5)	0	3 (14)	3 (16)
TEAE leading to treatment discontinuation, n (%)[e]	0	2 (14)	2 (10)	3 (16)

- The most common treatment-related TEAEs (any grade) were hypertension (12% of patients), bone pain (9%), and diarrhea (5%)
- Three grade 3 TEAEs were considered treatment related: single cases of hypertension, diarrhea, and dehydration
  - No treatment-related grade 4 or 5 TEAEs were reported
- Grade 3 hypertension was reported in 3 (4%) patients; none led to treatment discontinuation
  - No grade 4 hypertension events were reported
- One transformation to blast phase occurring after the end of treatment visit, but was not considered related to treatment

[a] In the 12 weeks prior to treatment. [b] A stable daily dose of RUX for ≤ 16 weeks at enrollment. [c] individual cases of diarrhea, enteritis, and urinary tract infection. [d] The 7 TEAEs leading to death were multiple organ dysfunction syndrome, pneumonia, septic shock, post-procedural hemorrhage, subdural hematoma, myelofibrosis, and ischemic stroke. [e] TEAEs were individual cases of anemia, splenomegaly, fatigue, general physical health deterioration, pyelonephritis, sepsis, urinary tract infection, and diverticular perforation.

SAE, serious adverse event.

SUMMARY

- The initial results from this ongoing study suggest clinical activity of luspatercept in patients with MF-associated anemia
- Luspatercept improved anemia in those receiving and not receiving RBC transfusions, with more profound effects in patients treated with RUX
- The majority of adverse events were grade 1–2 in severity, consistent with previous studies of luspatercept in myelodysplastic syndromes and β-thalassemia

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