# Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis: results from the ACE-536-MF-001 study

MPN-404


Aaron T. Gerds,[1] Claire Harrison,[2] Jean-Jacques Kiladjian,[3] Ruben Mesa,[4] Alessandro M. Vannucchi,[5] Rami Komrokji,[6] Prithviraj Bose,[7] Marina Kremyanskaya,[8] Adam J. Mead,[9] Jason Gotlib,[10] Fabian Sanabria,[11] Niloufar Marsousi,[11] Ana Carolina Giuseppi,[12] Huijing Jiang,[12] Jeanne M. Palmer,[13] Kelly McCaul,[14] Vincent Ribrag,[15] Francesco Passamonti[16]

[1]Cleveland Clinic, Cleveland, OH, USA; [2]Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Hôpital Saint-Louis, Paris, France; [4]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [5]AOU Careggi, Florence, Italy; [6]Moffitt Cancer Center, Tampa, FL, USA; [7]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [8]Mount Sinai Hospital, New York, NY, USA; [9]MRC Weatherall Institute of Molecular Medicine, NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; [10]Stanford Cancer Institute, Stanford, CA, USA; [11]Bristol Myers Squibb, Boudry, Switzerland; [12]Bristol Myers Squibb, Princeton, NJ, USA; [13]Mayo Clinic, Phoenix, AZ, USA; [14]University of Tennessee Medical Center, Knoxville, TN, USA; [15]Institut Gustave Roussy, Villejuif, France; [16]University of Milan Statale, Milan, Italy


## Introduction

- Approximately 40% of patients with myelofibrosis (MF) have anemia (hemoglobin [Hgb] < 10 g/dL) at diagnosis and nearly 25% are red blood cell (RBC) transfusion dependent (TD); many will develop chronic anemia, and transfusion dependency typically increases throughout the disease course[1]
  - RBC transfusions for anemia are an indicator of poor prognosis for patients with MF[2]
- Janus kinase (JAK) inhibitors, including ruxolitinib (RUX) and fedratinib, have become standard treatments for MF, but 23%–38% of patients experience grade 3/4 anemia while on these treatments, and anemia is a leading cause of RUX discontinuation[2,3]
- Luspatercept (LUSPA) is a first-in-class erythroid maturation agent that binds several tumor growth factor β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[4]
- LUSPA is approved by the US FDA for the treatment of anemia in some adults with β-thalassemia and myelodysplastic syndrome requiring RBC transfusion[7]
- The phase 2, multicenter, open-label ACE-536-MF-001 study (NCT03194542) evaluated the efficacy and safety of luspatercept (ACE-536) in patients with myeloproliferative neoplasm-associated MF and anemia with and without RBC transfusion dependence

## Methods

- Patients were enrolled and treated in 4 cohorts based on transfusion dependence and stable RUX treatment (**Figure 1**)
  - Patients were defined as TD if receiving 4-12 RBC units/84 days immediately preceding cycle 1 day 1
  - For non-transfusion dependent (NTD) patients, anemia was defined as ≥ 3 Hgb level measurements of ≤ 9.5 g/dL recorded on ≥ 3 different days in the 84-day period immediately preceding cycle 1 day 1
- Cohorts
  - 1: NTD, no RUX
  - 2: TD, no RUX
  - 3A: NTD, RUX
  - 3B: TD, RUX
- Patients received lupatercept 1.0 mg/kg subcutaneously with titration up to 1.75 mg/kg in 21-day cycles. Anemia response was assessed at day 169
- The primary endpoint was anemia response, defined as:
  - TD patients: 84 consecutive days without RBC transfusion
  - NTD patients: 84 consecutive days with Hgb increase of ≥ 1.5 g/dL from baseline without transfusion
- Secondary endpoints included time to and duration of anemia response, frequency of RBC transfusions and transfusion dependence, symptom response, and changes in mean Hgb
- Efficacy analyses were primarily conducted in the intent-to-treat (ITT) population, consisting of all enrolled patients regardless of whether they received LUSPA
- Safety analyses were performed with the safety population, consisting of all patients who were enrolled and received ≥ 1 dose of LUSPA

## Results

### Disposition and baseline characteristics

- Of 95 patients in the ITT population, 28 (29.5%) discontinued at day 169 due to lack of clinical benefit
  - Other reasons for discontinuation included loss of response (13.7%), lack of efficacy before day 169 (12.6%), and withdrawal by the patient (12.6%)
- Most (54.7%) patients had primary MF, intermediate-2 risk score (75.8%), and > 2 years since initial diagnosis (74.7%) (**Table 1**)
  - In cohorts 3A/3B, median duration of prior RUX therapy was 18.1 months
  - In cohorts 2/3B, 84.7% of patients had a baseline transfusion burden of 6-12 units/84 days
- Mean treatment duration for the entire treatment period was 42.8 weeks
- Mean length of cycles between doses was 22.1 days
- A total of 71 (74.7%) patients received the maximum dose of 1.75 mg/kg luspatercept

### Efficacy

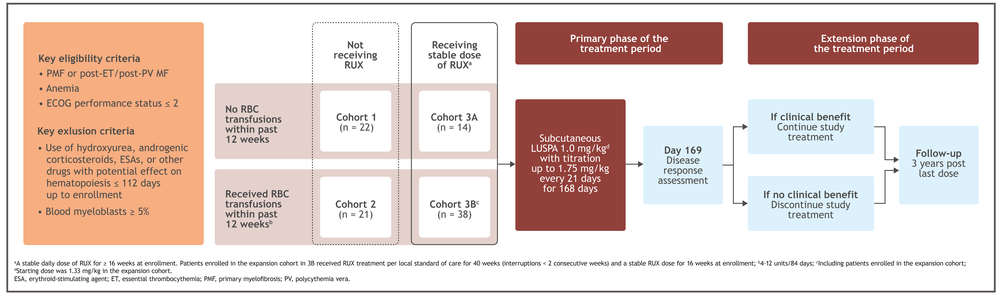
- Among NTD patients: anemia response rate in the primary treatment period was 13.6% in cohort 1 and 14.3% in cohort 3A (**Figure 2**)
  - Median time to achieve anemia response was 63 days in cohort 1 and 63.5 days in cohort 3A (**Table 2**)
  - The longest median duration of anemia response was 126 days in cohort 1 compared with 88.5 days in cohort 3A (**Table 2**)
  - Six (27.3%) patients in cohort 1 and 7 (50.0%) patients in cohort 3A achieved a mean Hgb increase of ≥ 1.5 g/dL from baseline in the entire treatment period (**Table 2**)
- Among TD patients, transfusion independence rate in the primary treatment period was 9.5% in cohort 2 and 26.3% in cohort 3B (**Figure 2**)
  - Median time to transfusion independence was 2 days in cohort 2 and 37 days in cohort 3B (**Table 2**)
  - The longest duration of anemia response was 623 days (mean) in cohort 2 and 448 days (median) in cohort 3B (**Table 2**)
    - Median for cohort 2 could not be calculated due to limited sample size
  - Three (14.3%) patients in cohort 2 and 8 (21.1%) patients in cohort 3B achieved a mean Hgb increase of ≥ 1.5 g/dL from baseline in the entire treatment period
  - Ten (47.6%) patients in cohort 2 and 20 (52.6%) patients in cohort 3B had ≥ 50% reduction in transfusion burden over any 84-day period in the entire treatment period
- Cohorts 3A and 3B (patients taking RUX at enrollment) had a higher proportion of patients with ≥ 50% reduction in MPN SAF TSS during the entire treatment period (cohort 3A, 21.4%; cohort 3B, 15.8%) compared with cohort 1 (9.1%) and cohort 2 (9.5%) (**Table 2**)
- Among patients receiving RUX:
  - In cohort 3A, 14 (100.0%) patients maintained RUX dose without modifications
  - In cohort 3B, 31 (81.6%) patients maintained or increased RUX dose without modifications
- At day 169, among patients with enlarged spleen at baseline, spleen size by palpation remained stable with no clinically meaningful variation across all 4 cohorts

### Safety

- A total of 89 (93.7%) patients experienced an adverse event (AE); 45 (47.4%) patients experienced treatment-related AEs (TRAEs) (**Table 3**)
  - Frequently reported AEs included hypertension (24.2%), diarrhea (24.2%), dyspnea (22.1%), thrombocytopenia (18.9%), and fatigue (17.9%)
  - The most frequently occurring TRAE was hypertension (17.9%)
    - Seven (7.4%) patients had grade ≥ 3 hypertension; all events were manageable with medical intervention and none resulted in LUSPA discontinuation
- Nine (9.5%) patients discontinued due to AEs; no AEs occurring in > 1 patient resulted in LUSPA discontinuation
- A total of 37 (38.9%) patients had ≥ 1 serious AE
  - Three (3.2%) patients had serious TRAEs (cerebral toxoplasmosis, urinary tract infection, and diarrhea [1 patient each])
  - Both cerebral toxoplasmosis and diarrhea occurred in patients also receiving RUX treatment
- Two (2.2%) patients had transformation to acute myeloid leukemia (AML); none were considered related to treatment
- A total of 9 (9.5%) patients died while on treatment; no deaths were considered related to treatment

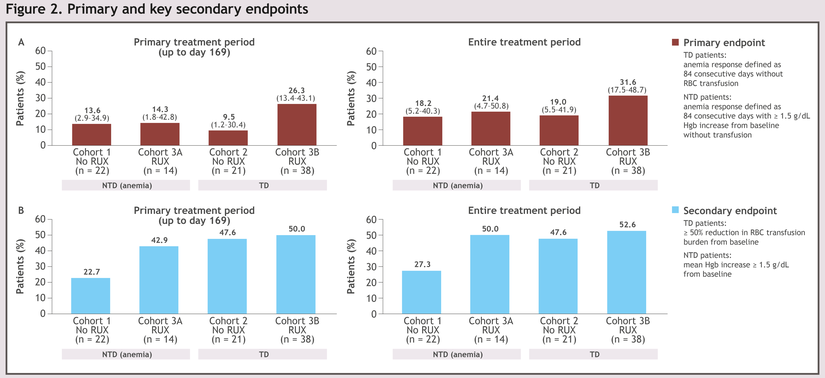
- In the phase 2 ACE-536-MF-001 study, LUSPA resulted in transfusion independence in TD patients and durable anemia response in NTD patients (Figure 2), demonstrating clinical benefit for patients in all 4 cohorts
  - Patients receiving RUX in combination with LUSPA (cohort 3) showed the greatest anemia response in the entire treatment period
    - TD patients (cohort 3B), 31.6% (95% CI, 17.5%–48.7%)
    - NTD patients (cohort 3A), 21.4% (95% CI, 4.7%–50.8%)
- Approximately half of TD patients receiving LUSPA achieved a 50% reduction in transfusion burden

**Figure 1. Study design**




[a]A stable daily dose of RUX for ≥ 16 weeks at enrollment. Patients enrolled in the expansion cohort in 3B received RUX treatment per local standard of care for 40 weeks (interruptions < 2 consecutive weeks) and a stable RUX dose for 16 weeks at enrollment; [b]4-12 units/84 days; [c]including patients enrolled in the expansion cohort; [d]Starting dose was 1.33 mg/kg in the expansion cohort.
ESA, erythroid-stimulating agent; ET, essential thrombocythemia; PMF, primary myelofibrosis; PV, polycythemia vera.

**Figure 2. Primary and key secondary endpoints**




Values above bars show % patients (95% CI [panel A only]).

**Table 1. Baseline demographics and disease characteristics[a]**

| | Cohort 1 No RUX NTD (n = 22) | Cohort 3A RUX NTD (n = 14) | Cohort 2 No RUX TD (n = 21) | Cohort 3B RUX TD (n = 38) | Total (N = 95) |
|---|---|---|---|---|---|
| **Age, years, median (min, max)** | 69.5 (50, 89) | 65.0 (51, 81) | 75.0 (60, 88) | 72.0 (59, 83) | 71.0 (50, 89) |
| **Male, n (%)** | 13 (59.1) | 7 (50.0) | 15 (71.4) | 23 (60.5) | 58 (61.1) |
| **Disease diagnosis, n (%)** | | | | | |
| PMF | 15 (68.2) | 6 (42.9) | 13 (61.9) | 18 (47.4) | 52 (54.7) |
| Post-PV *MF* | 0 | 4 (28.6) | 2 (9.5) | 7 (18.4) | 13 (13.7) |
| Post-ET *MF* | 7 (31.8) | 4 (28.6) | 6 (28.6) | 13 (34.2) | 30 (31.6) |
| **Time since initial diagnosis to first screening, n (%)** | | | | | |
| ≤ 2 years | 10 (45.5) | 2 (14.3) | 6 (28.6) | 6 (15.8) | 24 (25.3) |
| > 2 years | 12 (54.5) | 12 (85.7) | 15 (71.4) | 32 (84.2) | 71 (74.7) |
| **Time on RUX prior to study, months, median (min, max)[b]** | – | 16.4 (5.1, 71.8) | – | 18.8 (6.7, 150.6) | 18.1 (5.1, 150.6) |
| **DIPSS risk, n (%)** | | | | | |
| Intermediate risk 1 | 1 (4.5) | 4 (28.6) | 1 (4.8) | 3 (7.9) | 9 (9.5) |
| Intermediate risk 2 | 18 (81.8) | 9 (64.3) | 15 (71.4) | 30 (78.9) | 72 (75.8) |
| High risk | 2 (9.1) | 1 (7.1) | 5 (23.8) | 5 (13.2) | 13 (13.7) |
| Unknown | 1 (4.5) | 0 | 0 | 0 | 1 (1.1) |
| **Baseline transfusion burden, n (%)** | | | | | |
| <5 units/84 days | – | – | 1 (4.8) | 6 (15.8) | 7 (11.9) |
| 6-12 units/84 days | – | – | 18 (85.7) | 32 (84.2) | 50 (84.7) |
| > 12 units/84 days | – | – | 2 (9.5) | 0 | 2 (3.4) |

[a]Baseline is defined as the last value on or before the first dose of LUSPA, or average if multiple values are present for the same date; [b]Defined as sum durations of RUX on or prior to first LUSPA dose date, with overlapping periods excluded.
DIPSS, Dynamic International Prognostic Scoring System.

**Table 2. Secondary endpoints**

| | Cohort 1 No RUX NTD (n = 22) | Cohort 3A RUX NTD (n = 14) | Cohort 2 No RUX TD (n = 21) | Cohort 3B RUX TD (n = 38) |
|---|---|---|---|---|
| **Time to anemia response, days, median (min, max)[a]** | 63.0 (41.0, 68.0) | 63.5 (42.0, 85.0) | 2.0 (2.0, 2.0) | 37.0 (2.0, 71.0) |
| **Longest duration of transfusion independence, days[a]** | | | | |
| Mean (SD) | – | – | 623.0 (29.7) | 534.7 (527.67) |
| Median (min, max) | – | – | NA (602, 644) | 448.0 (85, 1582) |
| **Longest duration of Hgb increase ≥ 1.5 g/dL from baseline, days[a]** | | | | |
| Mean (SD) | 457.7 (611.2) | 88.5 (6.36) | – | – |
| Median (min, max) | 126.0 (84, 1163) | 88.5 (84, 93) | – | – |
| **Transfusion burden reduction, n (%)[c]** | | | | |
| Primary treatment period | – | – | 10 (47.6) | 19 (50.0) |
| Entire treatment period | – | – | 10 (47.6) | 20 (52.6) |
| **Mean Hgb increased ≥ 1.5 g/dL from baseline, n (%)** | | | | |
| Primary treatment period | 5 (22.7) | 6 (42.9) | 1 (4.8) | 5 (13.2) |
| Entire treatment period | 6 (27.3) | 7 (50.0) | 3 (14.3) | 8 (21.1) |
| **MPN SAF TSS ≥ 50% reduction from baseline, n (%)** | | | | |
| Primary treatment period | 2 (9.1) | 3 (21.4) | 2 (9.5) | 6 (15.8) |
| Entire treatment period | 2 (9.1) | 3 (21.4) | 2 (9.5) | 6 (15.8) |

[a]Time to anemia response for cohorts 1 and 3A defined as time between first administration of LUSPA and the first Hgb increase of ≥ 1.5 g/dL from a baseline starting an 84-day period of consecutive increase ≥ 1.5 g/dL without RBC transfusions. For cohorts 2 and 3B, defined as time between first administration of LUSPA and the first day of an RBC transfusion-free period of 84 days. Patient numbers for time to anemia response and duration of anemia response assessments as follows: cohort 1 (n = 3), cohort 3A (n = 2), cohort 2 (n = 2), cohort 3B (n = 10); [b]Duration of anemia response defined as last day of longest response - first date of longest response + 1; cohort 1 (n = 3), cohort 3A (n = 2), cohort 2 (n = 2), cohort 3B (n = 10); [c]Patients achieving ≥ 50% RBC transfusion burden reduction over any 84-day period.
MPN SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; NA, not available; SD, standard deviation.

**Table 3. Treatment-related adverse events**

| System organ class, preferred term[a] | Cohort 1 No RUX NTD (n = 22) | Cohort 3A RUX NTD (n = 14) | Cohort 2 No RUX TD (n = 21) | Cohort 3B RUX TD (n = 38) | Total (N = 95) |
|---|---|---|---|---|---|
| **Patients with ≥ 1 TRAE** | **14 (63.6)** | **7 (50.0)** | **5 (23.8)** | **19 (50.0)** | **45 (47.4)** |
| **Vascular disorders[b]** | 4 (18.2) | 4 (28.6) | 1 (4.8) | 8 (21.1) | 17 (17.9) |
| Hypertension | 4 (18.2) | 4 (28.6) | 1 (4.8) | 8 (21.1) | 17 (17.9) |
| **Musculoskeletal and connective tissue disorders** | 4 (18.2) | 3 (21.4) | 2 (9.5) | 4 (10.5) | 13 (13.7) |
| Bone pain | 2 (9.1) | 3 (21.4) | 2 (9.5) | 0 | 7 (7.4) |
| **Gastrointestinal disorders** | 4 (18.2) | 0 | 4 (19.0) | 4 (10.5) | 12 (12.6) |
| Diarrhea | 1 (4.5) | 0 | 2 (9.5) | 3 (7.9) | 6 (6.3) |
| **General disorders and administration site conditions** | 3 (13.6) | 1 (7.1) | 0 | 7 (18.4) | 11 (11.6) |
| **Investigations** | 1 (4.5) | 2 (14.3) | 2 (9.5) | 2 (5.3) | 7 (7.4) |
| **Metabolism and nutrition disorders** | 2 (9.1) | 0 | 2 (9.5) | 3 (7.9) | 7 (7.4) |
| **Nervous system disorders** | 1 (4.5) | 0 | 1 (4.8) | 4 (10.5) | 6 (6.3) |
| **Blood and lymphatic system disorders** | 0 | 0 | 2 (9.5) | 2 (5.3) | 4 (4.2) |
| **Infections and infestations** | 1 (4.5) | 0 | 1 (4.8) | 2 (5.3) | 4 (4.2) |
| **Respiratory, thoracic, and mediastinal disorders** | 0 | 0 | 1 (4.8) | 1 (2.6) | 2 (2.1) |
| **Eye disorders** | 0 | 0 | 1 (4.8) | 0 | 1 (1.1) |
| **Renal and urinary disorders** | 1 (4.5) | 0 | 0 | 0 | 1 (1.1) |
| **Skin and subcutaneous tissue disorders** | 0 | 0 | 1 (4.8) | 0 | 1 (1.1) |

[a]Values listed as n (%), only preferred terms occurring in > 5% of patients shown; total of preferred terms may not equal system organ class total; [b]All cases were hypertension.

## Conclusions

- In the ACE-536-MF-001 study, LUSPA demonstrated anemia improvement across all cohorts of patients with MF, regardless of transfusion dependency and use of RUX
  - In the primary treatment period, 9.5% and 26.3% of patients in cohorts 2 and 3B achieved transfusion independence; 13.6% and 14.3% of patients in cohorts 1 and 3A achieved anemia response, respectively
  - Approximately half of the patients in cohorts 2 and 3B had 50% transfusion burden reduction, and both cohorts achieved a mean duration of > 500 days transfusion independence
  - Approximately one-fourth of patients in cohort 1 and half of the patients in cohort 3A achieved mean Hgb increase ≥ 1.5 g/dL from baseline
- Most patients receiving RUX with LUSPA maintained or were able to increase their dose of RUX
- The safety profile of LUSPA was consistent with previous studies
  - No new safety signals were identified
  - Hypertension was the most common TRAE, but cases were generally low grade and manageable, and did not result in LUSPA discontinuation
  - Transformation rates to AML were low (2 patients, 2.2%) and unrelated to study treatment
  - No deaths were related to LUSPA
- The effect of LUSPA as an erythroid maturation agent appeared to be consistent in patients with MF as in patients with other approved indications[8]
- These results warrant continued study of LUSPA in MF-associated anemia in TD patients receiving concomitant JAK2 inhibitor therapy in the phase 3 INDEPENDENCE study (ACE-536-MF-002)

### References


1. Tefferi A, et al. *Mayo Clin Proc* 2012;87:25-33.
2. Elena C, et al. *Haematologica* 2011;96:167-170.
3. Kuykendall AT, et al. *Annals Hematol* 2018;97:435-441.
4. Harrison CN, et al. *Leukemia* 2016;30:1701-1707.
5. Harrison CN, et al. *Am J Hematol* 2020;95:594-603.
6. Suragani RNVS, et al. *Nat Med* 2014;20:408-414.
7. REBLOZYL® (luspatercept-aamt) [package insert]. Summit, NJ: Celgene Corporation; September 2022.
8. Fenaux P, et al. *N Engl J Med* 2020;382:140-151.


### Acknowledgments


- The patients and families who are making the study possible
- The clinical study teams who participated
- Study drugs were provided by Bristol Myers Squibb (Princeton, NJ, USA)
- The sponsor did not supply RUX for this study. Instead, RUX was obtained by the sites according to local clinical study agreement and in accordance with local guidelines
- The study was supported by Bristol Myers Squibb
- All authors contributed to and approved the presentation
- Writing and editorial assistance were provided by Katie Walwyn-Brown, PhD, of Caudex, funded by Bristol Myers Squibb

Previously presented at the American Society of Clinical Oncology Meeting; June 2-6, 2023; Chicago, IL & Online (Poster 7016) and at the European Hematology Association Meeting; June 8-11, 2023; Frankfurt, Germany (Oral S167)


Scientific Content on Demand

To request a copy of this poster:

Scan QR code via a barcode reader application

QR codes are valid for 90 days after the congress presentation date.




Copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission from the author of this poster