

THE SAFETY PROFILES OF ESAs AT DIFFERENT HEMOGLOBIN LEVELS

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INTRODUCTION

- Erythropoiesis-stimulating agents (ESAs) are standard therapy for the management of renal anemia, and are associated with improved quality of life and reduced need for transfusions in patients with chronic kidney disease (CKD).¹
- Recent studies, however, have raised concerns about the safety of ESAs at hemoglobin (Hb) levels >13.0 g/dL,^{2,3} suggesting an increased risk of cardiovascular events when targeting Hb levels >13.0 g/dL. This has led to a reappraisal of upper limits of Hb in patients with renal anemia.
- C.E.R.A. (MIRCERA®)**, a continuous erythropoietin receptor activator, is a new, long-acting ESA that is approved for the treatment of anemia in patients with CKD. The **MIRCERA** Phase III clinical program, the largest ever undertaken in renal anemia management, involved ~2400 patients with CKD who were treated with either **MIRCERA** or a reference ESA (epoetin alfa, epoetin beta or darbepoetin alfa). The program provided a large amount of safety data that have been analyzed across the full range of Hb levels to assess possible trends in the occurrence of safety events.

PURPOSE

- To analyze, using pooled data from the **MIRCERA** Phase III clinical program, the relationship between safety events and Hb level and to determine whether the data are consistent with recent regulatory guidance.

PATIENTS

- Data were pooled from six Phase III correction (AMICUS, ARCTOS) and maintenance (MAXIMA, PROTOS, RUBRA, STRIATA) studies with similar inclusion and exclusion criteria:
 - Major inclusion criteria: patients aged ≥18 years with CKD; baseline Hb between 8.0-11.0 g/dL (correction studies) or 10.5-13.0 g/dL (maintenance studies); adequate iron status (serum ferritin ≥100 ng/mL or transferrin saturation ≥20% or hypochromic red cells <10%).
 - Major exclusion criteria: blood transfusion within the 12 weeks preceding randomization; non-renal causes of anemia; C-reactive protein >30 mg/L; life expectancy <12 months.

METHODS

- The six Phase III studies were randomized, controlled, international, multicenter open-label trials. Details of study designs and outcomes have been reported previously.⁴⁻⁹
- For the correction studies, ESA doses were adjusted to achieve a Hb response (defined as an increase in Hb ≥1.0 g/dL from baseline and Hb ≥11.0 g/dL without blood transfusion during the first 24 [AMICUS] or 28 weeks [ARCTOS] after the first dose) and then to maintain individual patient Hb within ±1.0 g/dL of response level and between 11.0-13.0 g/dL.

- For the four maintenance studies, ESA doses were adjusted to maintain Hb within ±1.0 g/dL of the baseline and between 10.0-13.5 g/dL during the titration and evaluation periods; in MAXIMA, PROTOS and STRIATA Hb was kept between 11.0-13.0 g/dL during the long-term safety period.
- Safety parameters analyzed in the pooled population included all adverse events (AEs), serious AEs, AEs leading to death and deaths. The distribution of Hb and safety parameters was summarized based on the numbers and percentages of events within each Hb category, and the last Hb within a 4-week time period before the onset of an event was used to link it to a specific Hb category.
- A risk ratio (RR) was calculated from the percentage distribution of events within Hb categories and the proportion of Hb values within each category; the RR is the ratio of the two percentages. The 95% confidence intervals (CIs) of the RRs were calculated and examined for a possible association of the Hb category and safety findings. A possible association was identified if the lower limit of the CI was above 1.

AEs of special interest

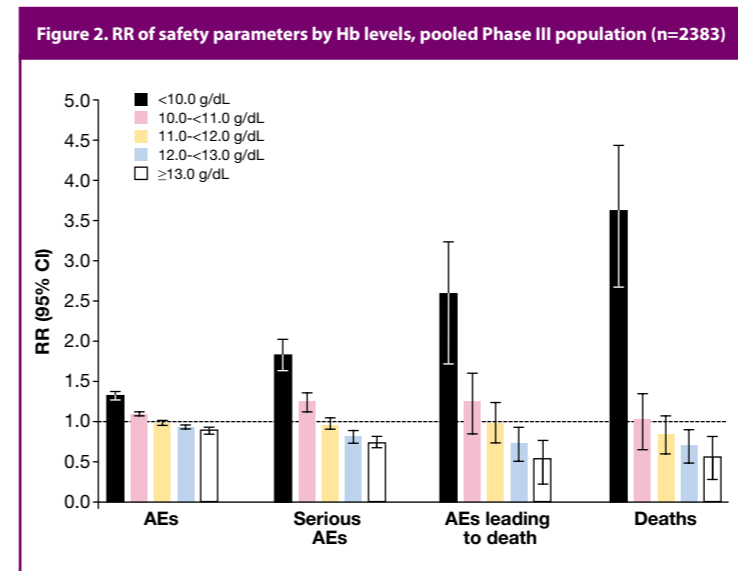
- The distribution of AEs of special interest was assessed using the same methodology. These AEs were defined based on the safety profile of patients with renal anemia treated with ESAs.
- AEs of special interest included hypertension, vascular access thrombosis (VAT), arrhythmia, congestive heart failure (CHF), sepsis, myocardial infarction (MI), occlusive cerebrovascular accident (CVA), cardiac arrest, deep vein thrombosis/pulmonary embolism (DVT/PE), seizures, and other thromboembolic events (TEEs).

RESULTS

- The pooled population consisted of 2383 patients with CKD both on dialysis and not on dialysis who were treated with either MIRCERA (n=1435), comparator ESA (epoetin [n=630] or darbepoetin alfa [n=318]) for Hb correction or maintenance (Table 1).

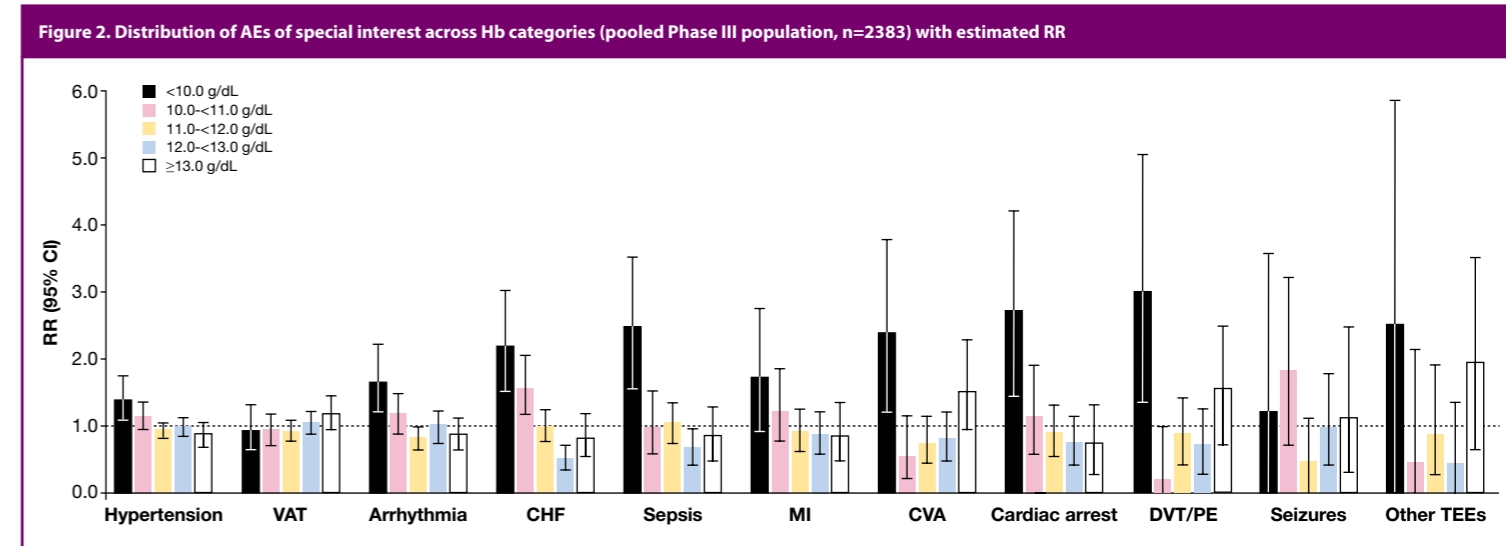
Table 1. Overview of patient population	
	Pooled Phase III population (n=2383)
Male, n (%)	1383 (58.0)
Age (years), mean (SD)	60.5 (15.0)
Age category, n (%)	
<65	1332 (55.9)
65-74	557 (23.4)
>74	494 (20.7)
Race, n (%)	
Caucasian	1712 (71.8)
Black	472 (19.8)
Oriental	136 (5.7)
Other	63 (2.6)
Baseline Hb (g/dL), mean (SD)	
Correction	9.9 (0.8)
Maintenance	11.8 (0.7)
Study design, n (%)	
Correction	504 (21.1)
Maintenance	1879 (78.9)
Mode of dialysis, n (%)	
Hemodialysis	1988 (83.4)
Peritoneal dialysis	71 (3.0)
Not yet on dialysis	324 (13.6)

- There was a consistent trend to higher risks of mortality, AEs, serious AEs and AEs leading to death with lower Hb values, with the highest RRs for all event categories observed at Hb levels <10.0 g/dL (Figure 1). The lower limit of the 95% CI for the RR of Hb <10.0 g/dL exceeded 1 in each of the categories death, AEs, serious AEs and AEs leading to death.



AEs of special interest

- The same was true for 7 of the 11 categories of AEs of special interest. The lower limit of the 95% CI for the RR of Hb <10.0 g/dL was above 1 for hypertension, arrhythmia, CHF, sepsis, occlusive CVA, cardiac arrest and DVT/PE. Most of the other categories of AEs of special interest also showed the highest RR at Hb <10.0 g/dL, and many of these showed the next highest RR at Hb 10.0-11.0 g/dL. One exception was VAT, where the lowest RR was in the Hb category <10.0 g/dL and the highest RR was in the highest Hb category, although the lower limit of the CI was below 1 (Figure 2).



CONCLUSIONS

- In this large clinical program, a consistent trend to increased risks of safety events (mortality, AEs, serious AEs, and AEs leading to death) was observed with lower Hb levels. Large studies in the medical literature have reported similar findings.¹⁰⁻¹²
- Almost all AEs of interest (hypertension, arrhythmia, CHF, sepsis, MI, occlusive CVA, cardiac arrest, DVT/PE, and other TEEs) had the highest RR at Hb <10.0 g/dL and many had the second highest RR in the Hb category 10.0-11.0 g/dL.
- One exception was VAT, where the highest RR was in the highest Hb category; a finding reported in other published studies.^{13,14} However, in our data this finding was not substantiated by an analysis of CI, since the lower limit of the CI was below 1.
- Our safety data support the 11.0-12.0 g/dL Hb target recommended by current KDOQI guidelines.¹⁵

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