

October 18, 2010

Testimony of Wolfgang C. Winkelmayer, MD, ScD, FASN on behalf of ASN at the:

Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee (CRDAC)  
meeting on “RESULTS OF THE TRIAL TO REDUCE CARDIOVASCULAR EVENTS WITH  
ARANESP® THERAPY (TREAT)”

*[Slide 1: ASN logo, WCW name and position]*

Dear Chairman, Ladies and Gentlemen:  
My name is Dr. Wolfgang Winkelmayer.

*[Slide 2: ASN logo, mission statement]*

I am speaking today on the behalf of the American Society of Nephrology, a large not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease.

Anemia is a common complication in patients with advanced chronic kidney disease (or CKD) and occurs in most patients even before they require chronic dialysis treatment. Prior to the availability of erythropoietin treatment, patients with advanced CKD were often anemic and blood transfusions were common. Epoetin was approved by the FDA based on studies demonstrating its efficacy in reducing the requirement for blood transfusions. Availability of the drug for clinical use in 1989 led to a demonstrable effect on reduced transfusion rates on a population level.

As you are deliberating today on how the evidence from TREAT may warrant a change in the current label of darbepoetin and epoetin, we would like to emphasize three important points:

*[Slide 3: TREAT supports the current label.]*

First, we would like to highlight that the results from TREAT are perfectly compatible with results from the previous trials, CREATE, CHOIR, and – in CKD patients undergoing dialysis – the Normal Hematocrit Study. All four trials have consistently shown that if a population is being treated to a target hemoglobin above the upper limit of the current label, 12 g/dL, no meaningful benefits arise and adverse outcomes may occur.

*[Slide 4: The TREAT Placebo Group Conundrum]*

Secondly, we would like to argue that TREAT does not provide evidence that would support reducing the current lower range of the labeled target hemoglobin below 10 g/dL. TREAT

intended to study a population of patients with advanced chronic kidney disease and anemia, with the expectation that the patients' kidney function and – correspondingly – anemia would deteriorate during follow up. By contrast, the study population's anemia status *improved* during follow up, as illustrated in the placebo group. Starting from an enrollment median hemoglobin of 10.4 g/dL, the mean hemoglobin concentration increased during follow-up, with a mean time-averaged hemoglobin of 10.6 g/dL. Less than half of the patients did not require any darbepoetin treatment and of those who did, most received only a single dose. Thus, for a variety of reasons, TREAT ended up enrolling a healthier population than anticipated, with the majority of patients not necessary requiring any ESA treatment, even under the ramifications of the current label. Thus, we argue that the inferences that can be made from TREAT about the optimal label range are limited and any justification for a label change based on TREAT is inherently weak. A comparison of achieved mean hemoglobin concentrations among the 4 large ESA trials puts the low hemoglobin groups in each of them well within the range of the current label.

*[Slide 5: Consequences of Lowering the Labeled Hemoglobin Target Range]*

Third, assume that the label be adjusted to contain a reduced lower hemoglobin boundary and consider the likely consequences. Patients with CKD would be closer to what providers might consider a transfusion threshold. With many of these patients being potential candidates for future kidney transplantation, higher exposure to transfusions would translate into increased risks of immune-sensitization, which would then reduce their likelihood of receiving and successfully maintaining a functioning kidney transplant. Importantly, lowering the labeled hemoglobin target would put women and minorities at particular risk. Such a policy has the potential to create new and aggravate existing disparities in the access to kidney transplantation.

*[Slide 5: ASN Logo and Mission Statement]*

In summary, the ASN supports the current label, which is grounded in the best evidence currently available and has been adequate to support individualized treatment decisions among patients and their physicians.

Thank you on behalf of the ASN for the opportunity to explain our position today.



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# ASN Mission

ASN leads the fight against kidney disease by  
educating health professionals,  
sharing new knowledge,  
advancing research, and  
advocating the highest quality care



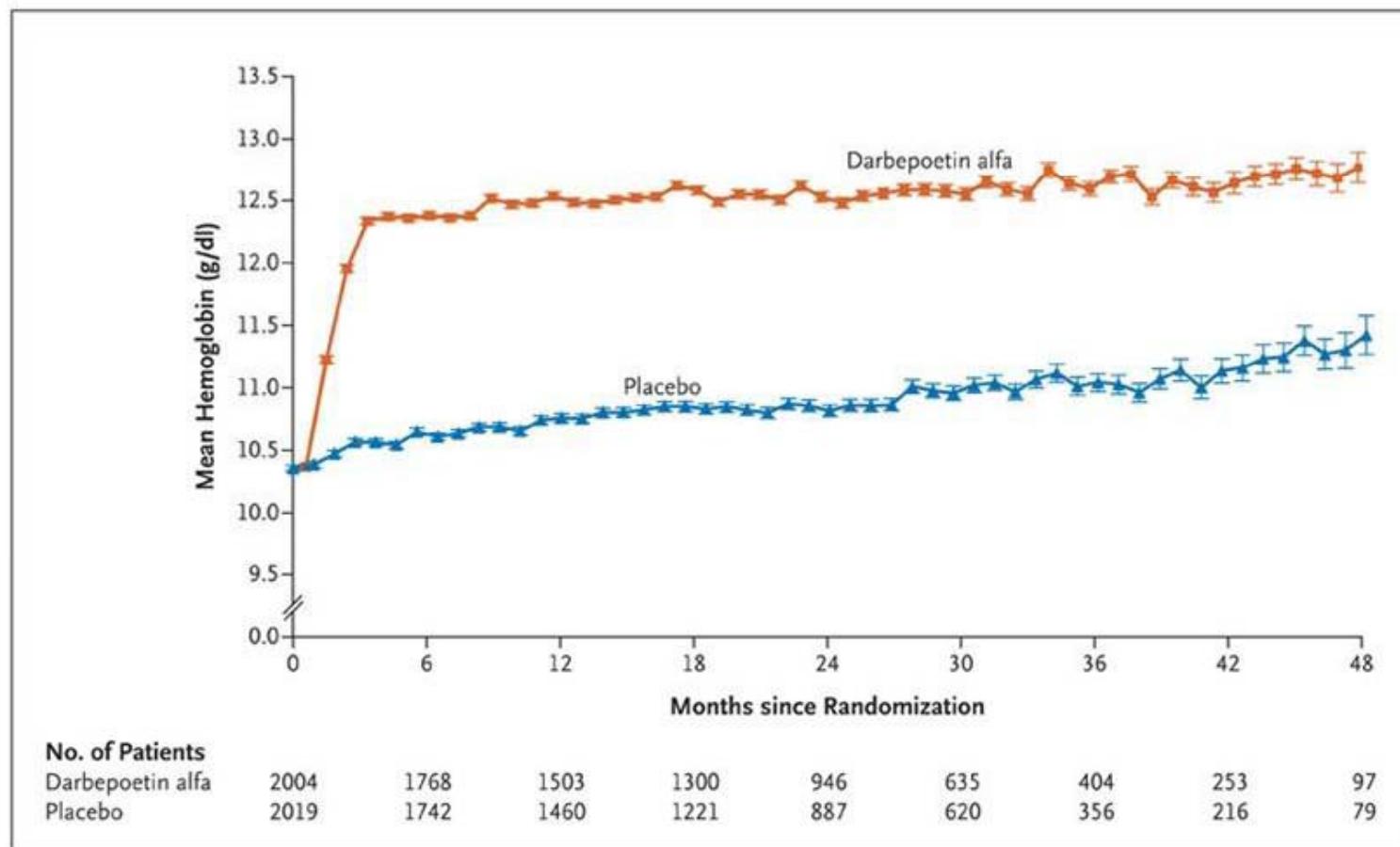
# TREAT Supports the Current Label

	Target hemoglobin g/dL		Achieved hemoglobin g/dL	
	Low	High	Low	High
Besarab	10	14	10.3	13.3
Drueke	11-12.5	13-15	11.5	13.5
Singh	11.3	13.5	11.4	12.8
Pfeffer	>9 *	13	10.6	12.5

\* Not a target; placebo group with rescue darbepoetin

Winkelmayr WC. *Semin Dial* 2010

# The TREAT Placebo Group Conundrum



Pfeffer MA, et al. NEJM 2009

# Consequences of Lowering the Labeled Hemoglobin Target Range

- Increased Risk of Transfusions
- Increased Risk of Immune-Sensitization
  - Creates Barriers to Kidney Transplantation
  - Lowers Chances of Long-Term Transplant Function
- May aggravate existing disparities in the access and outcomes of kidney transplantation
  - Women
  - African Americans



# Conclusions

1. Data from TREAT and other recent studies are consistent with the current labeled target hemoglobin of 10-12 g/dL
  
2. Given the complexity of chronic kidney disease, maintaining the integrity of the patient - physician relationship is essential to providing the highest quality of care.



**ASN** LEADING THE FIGHT  
AGAINST KIDNEY DISEASE