Erythropoiesis-Stimulating Agent (ESA) Therapy in Chronic Renal Failure (CRF)

Joint Meeting Between the
Cardiovascular and Renal Drugs &
Drug Safety and Risk Management
Advisory Committees

11 September 2007

Presentation Outline

TREAT	**Marc Pfeffer, MD, PhD** Dzau Professor of Medicine, Harvard Medical School, Cardiovascular Division, Brigham and Women's Hospital
Introduction	**Paul Eisenberg, MD, MPH, FACC** Global Regulatory Affairs & Safety, Amgen Inc
Clinical Perspective	**Allen R. Nissenson, MD, FACP, FASN** Professor of Medicine, Associate Dean, Director, Dialysis Program, David Geffen School of Medicine, UCLA
Benefit/Risk	**Preston Klassen, MD, MHS** Global Development, Amgen Inc
Risk Management	**Paul Eisenberg, MD, MPH, FACC** Global Regulatory Affairs & Safety, Amgen Inc

Amgen and J&JPRD Guests

Fredric Finkelstein, MD	Chief of Nephrology, Hospital of St. Raphael Clinical Professor of Medicine, Yale University School of Medicine
Patrick Marquis, MD, MBA	Global Director, Mapi Values
Kenneth J. Rothman, DrPH	Vice President of Epidemiology Research, RTI Health Solutions
Donald B. Rubin, PhD	John L. Loeb Professor of Statistics, Harvard University
Robert J. Rubin, MD	Clinical Professor of Medicine, Georgetown University
Theodore Steinman, MD	Professor of Medicine, Harvard Medical School, Nephrologist, Beth Israel Deaconess Medical Center
John E. Ware, Jr., PhD	Research Professor, Tufts School of Medicine, Senior Scientist and CEO, QualityMetric Incorporated
James B. Young, MD	Professor and Chairman, Division of Medicine, Cleveland Clinic Foundation

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Randomized Trials of ESAs in CRF

Marc A. Pfeffer MD, PhD

Dzau Professor of Medicine

Harvard Medical School, Cardiovascular Division, Brigham and Women's Hospital

Chair, TREAT Executive Committee

TREAT: Executive Committee and DSMC

Executive Committee

- E Burdmann
- M Cooper
- KU Eckhardt
- AS Levey
- J McGill
- J McMurray
- P Parfrey
- HH Parving
- M Pfeffer (Chair)
- G Remuzzi
- A Singh
- S Solomon
- R Toto
- D de Zeeuw

DSMC

- G Chertow
- D DeMets (Chair, SDAC)
- E Frohlich
- C Hennekens (Chair)
- P O'Brien
- J Rouleau

ESA RCTs in CRF

		CREATE	CHOIR	TREAT
Design		Randomized, open-label	Randomized, open-label	Randomized, double-blind, placebo-controlled
Agent		NeoRecormon® (epoetin beta)	PROCRIT® (Epoetin alfa)	Aranesp® (darbepoetin alfa)
Hb Target(s), g/dL	Arm 1	13.0-15.0	13.5	13.0
	Arm 2	10.5-11.5*	11.3	Placebo; rescue for Hb <9.0
N		603	1432	(planned ~4000)
Primary Composite Endpoint		All-cause mortality or CV morbidity: MI, HF, stroke, TIA, angina, arrhythmia or PVD complications	All-cause mortality or CV morbidity: MI, Stroke, HF hospitalization (without RRT)	All-cause mortality or CV morbidity: MI, Stroke, HF requiring medical attention, Myocardial Ischemia
No. of Endpoints		105	222	Projected: 1203
Censor at RRT		No	Yes	No

*Treatment starts when Hb <10.5 g/dL

TREAT: Trial to Reduce Cardiovascular Events with Aranesp® (Darbepoetin alfa) Therapy

Hypothesis:

Treatment of anemia with Aranesp® reduces the risk of mortality and nonfatal cardiovascular events (stroke, HF requiring medical attention, MI, or myocardial ischemia) in patients with CKD and type 2 diabetes

Study Population
- Hb ≤11 g/dL
- eGFR 20-60 mL/min/1.73m^2
- Type 2 DM

Design – randomized (1:1), **double-blind**, controlled

N = 2000 — Aranesp® Group (Target Hemoglobin 13 g/dL)

N = 2000 — **Placebo** (rescue if Hb<9 g/dL)

Event-driven: 1203 patients with events

CHOIR Results

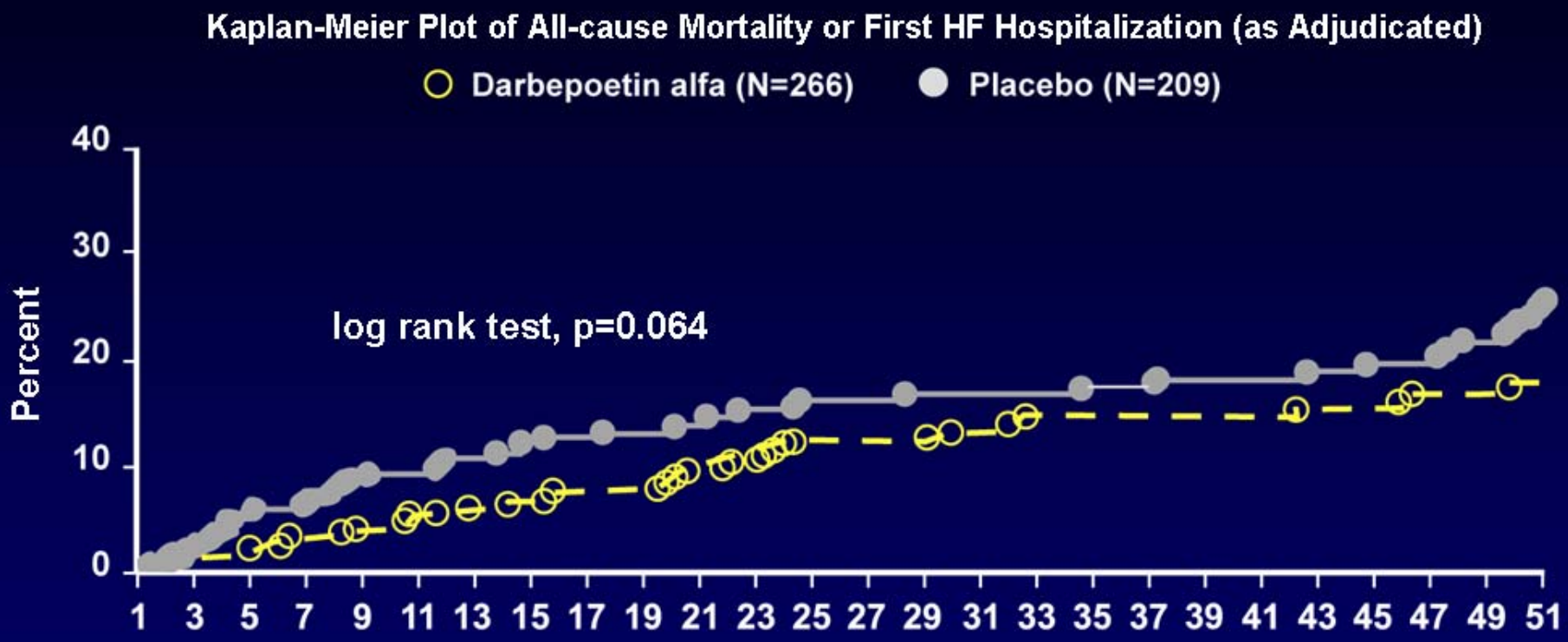
	Number of Events			
	High Hb N=715	Low Hb N=717	HR	P-value
Primary Endpoint	125	97	1.34 (1.03, 1.74)	0.03
KM—3 yr event rate	29.5%	24.9%		
Death	52	36	1.48 (0.97, 2.27)	0.07
CHF hospitalization (without RRT)	64	47	1.41 (0.97, 2.05)	0.07
Stroke	12	12	1.01 (0.45, 2.25)	0.98
MI	18	20	0.92 (0.48, 1.73)	0.78

Singh A et al. *NEJM*. 2006.

TREAT Response to CHOIR

- Preliminary CHOIR data released April 2006
  - DSMC and sites updated May 2006
  - Informed Consent updated June 2006
- CHOIR data published in NEJM November 2006
  - DSMC and sites updated November 2006
- US Aranesp® label changed March 9th, 2007
  - Executive Committee briefed sites and DSMC on US label changes
  - Informed Consent updated
- In May 2007, Executive Committee requested that the DSMC adopt a very conservative stopping rule for harm (one sided $p<0.05$ at any time)
- On July 18th, 2007 the DSMC met and found no cogent reasons to recommend alteration or termination of TREAT
- It can be inferred that the HR for harm did not exceed 1.16

Phase 2 HF Results Suggest Improved Outcome with Darbepoetin alfa Treatment Targeted to Normalize Hb



Outcomes Measures	Hazard Ratio (95% CI)
Composite morbidity & mortality	0.67 (0.44, 1.03)
All-cause mortality	0.76 (0.39, 1.48)
HF hospitalization	0.66 (0.40, 1.07)

Studies 20010170 and 20020171

RED-HF Trial Study Design

Hypothesis:

Treatment with darbepoetin alfa in subjects with symptomatic left ventricular systolic dysfunction and anemia decreases the risk of all-cause mortality or hospital admission for worsening HF

Study Population

- 9 ≤ Hb ≤12 g/dL
- LVEF ≤ 40%
- NYHA Class II to IV

Design – randomized (1:1), **double blind**, controlled

- N = 1700 — **Darbepoetin alfa group** (target Hb 13.0 g/dL, not to exceed 14.5 g/dL)
- N = 1700 — **Placebo** (rescue if Hb<9 g/dL)

Event driven: ~1450 primary events

Primary Endpoint*

- Time to death from any cause or first hospital admission for worsening HF, whichever is first

*Endpoint events are adjudicated by an independent clinical endpoint committee

Total Subject Exposure and Endpoints in TREAT Exceed CHOIR

Study	N	Total (Patient years)	Events
CREATE	603	1763	105
CHOIR	1432	1943	222
TREAT	3789*	4920*	514* (1203 projected)

*As of 1 Sep 07

Importance of TREAT

- **TREAT addresses the proper question**
  - Hypothesis even more important than when we started
- **Appropriate (well-treated) patient population**
- **Enrollment nearly complete (largest sample size)**
- **High compliance**
- **High follow-up**
- **Event rates are on track (largest number of adjudicated CV endpoints)**

Uncertainty can only be addressed by robust RCT data

Summary

- TREAT and RED-HF will provide a sufficient totality of evidence on which to base the most rational judgments for individual patients and the health of the general public
- In the meanwhile the sponsors are proposing reasonable and useful guidelines for risk management of patients receiving ESA therapy