

Antalya May 20, 2010



**12° National Congress of Turkish Society of
Hypertension and Renal Disease**

**Current situation and future
of renal anemia treatment.**

FRANCESCO LOCATELLI

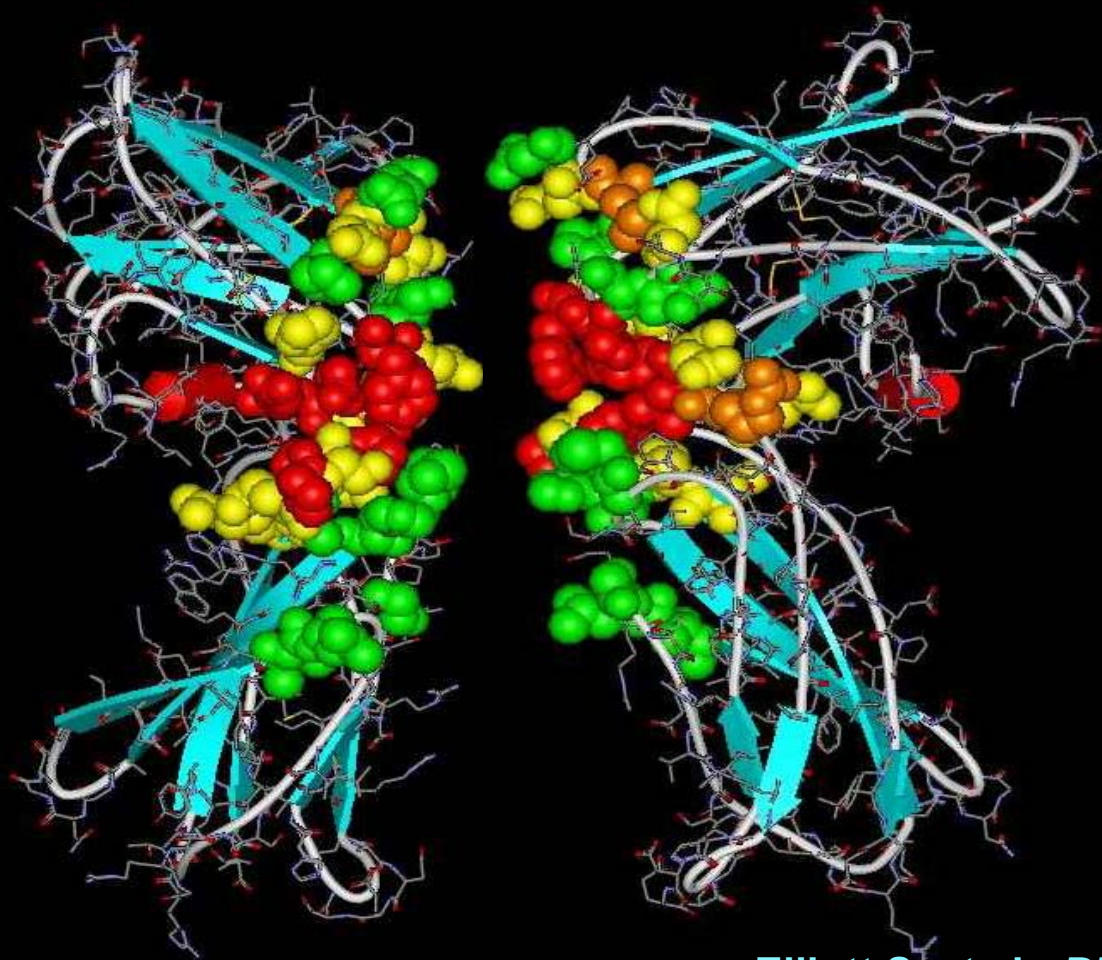
Department of Nephrology, Dialysis and Renal Transplantation

A Manzoni Hospital, Lecco, Italy

Erythropoietin has two erythropoietin receptor binding sites

EPO receptor

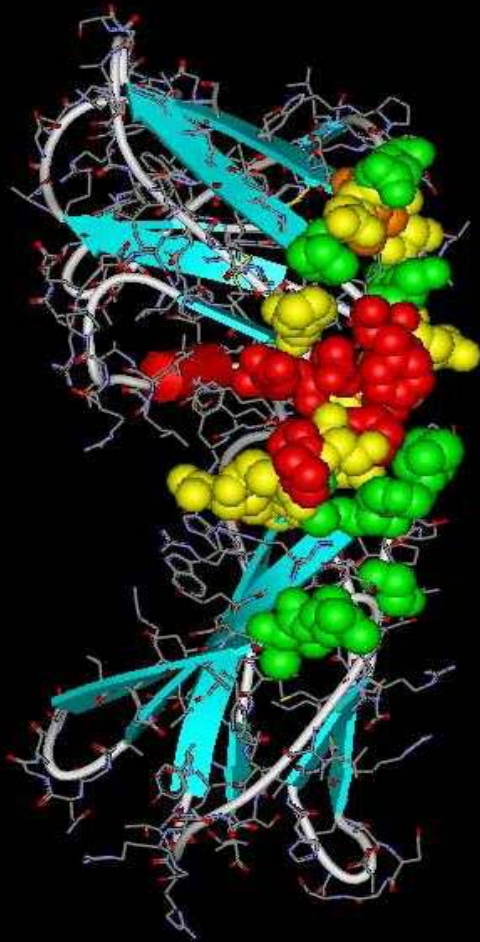
EPO receptor



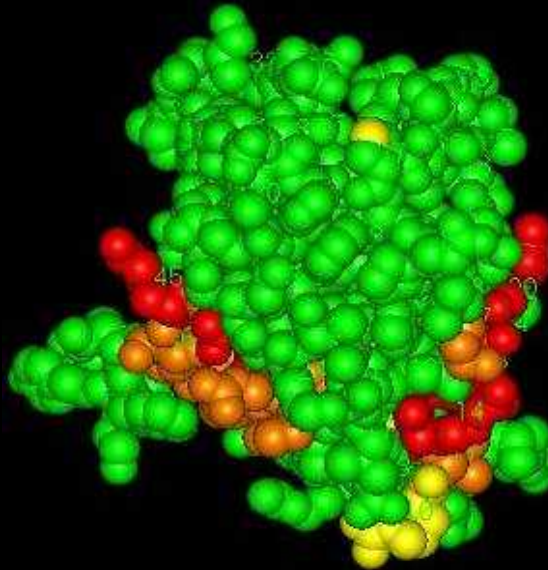
Elliott S, et al. *Blood* 89: 493-502, 1997
Syed RS, et al. *Nature* 395: 511-516, 1998

Erythropoietin has two erythropoietin receptor binding sites

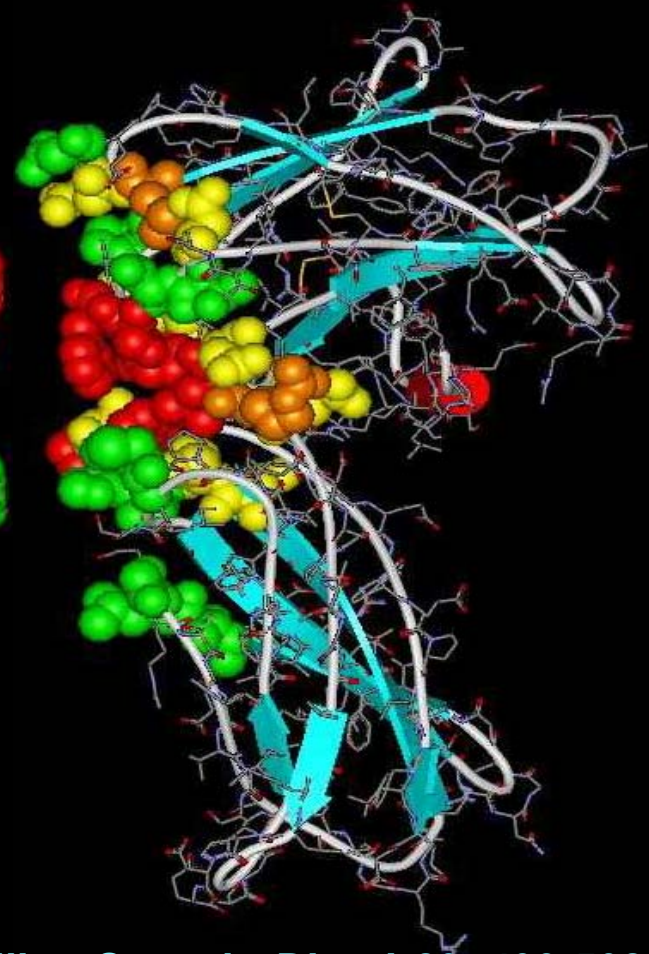
EPO receptor



rHuEPO



EPO receptor



Elliott S, et al. *Blood* 89: 493-502, 1997
Syed RS, et al. *Nature* 395: 511-516, 1998

The ideal ESA

- **Effective**
- **Safe**
- **Flexible administration route**
- **Less frequent administration schedule**
- **Cheap**

Currently available ESAs

- **Recombinant human erythropoietin (rHuEPO)**

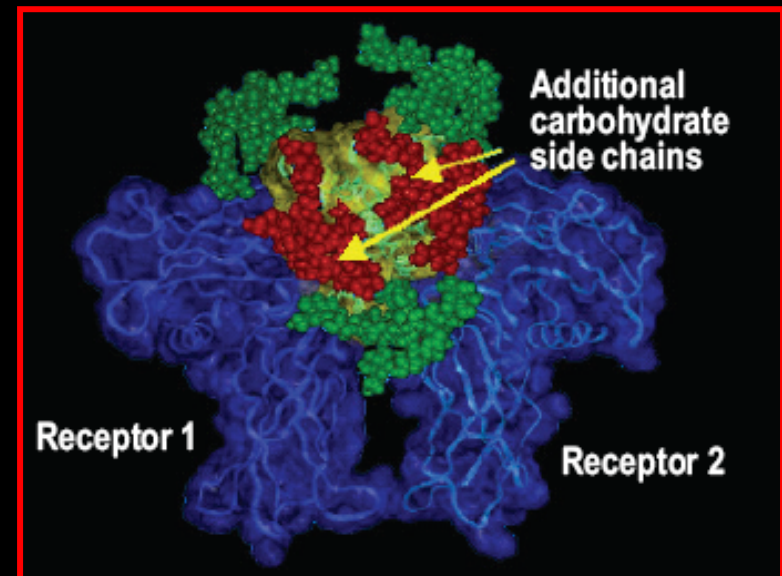
- Epoetin alfa
- Epoetin beta

- **Long-acting ESAs**

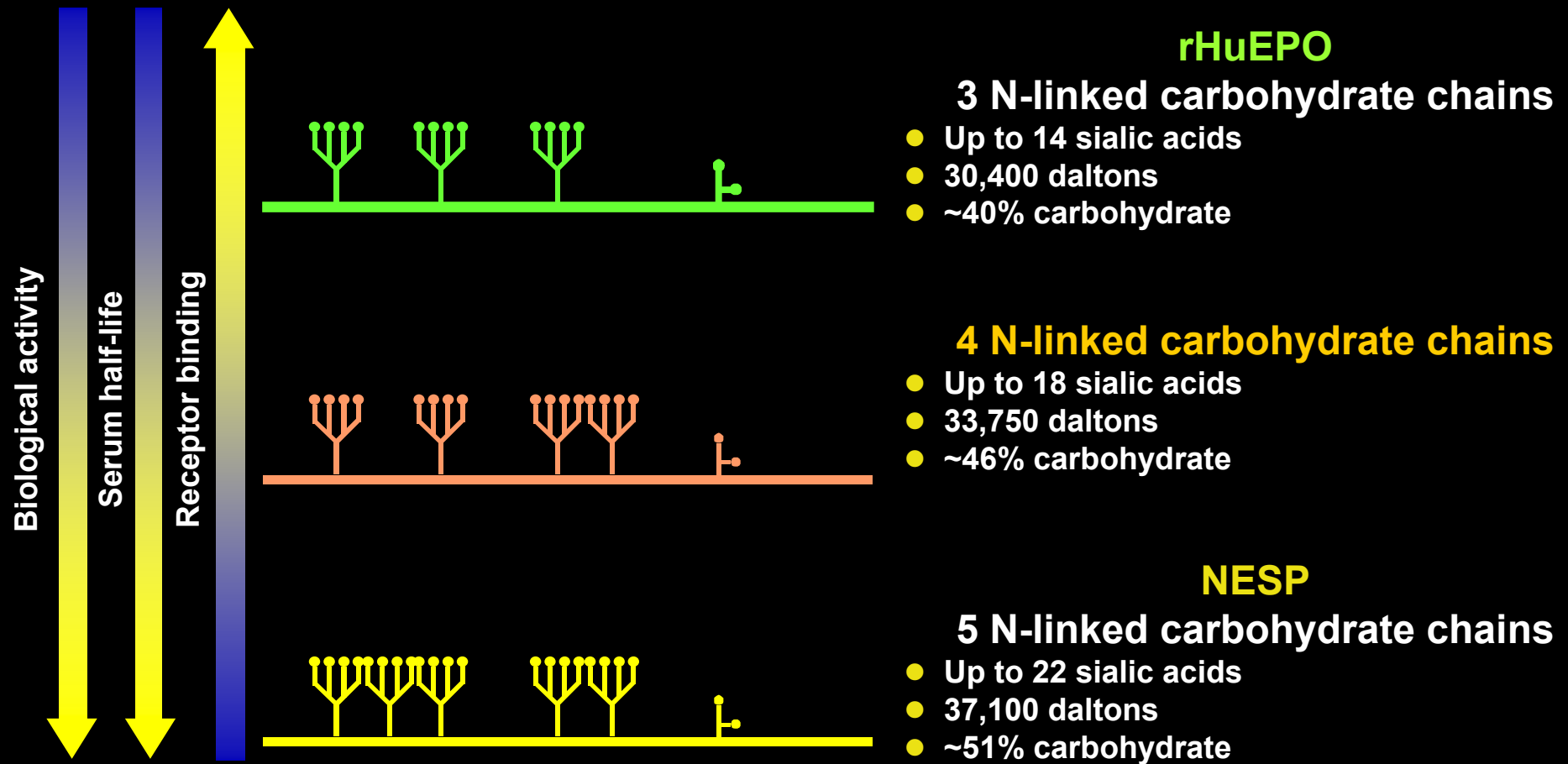
- Darbepoetin alfa
 - Different molecular structure
 - Increased biological activity

- **CERA**

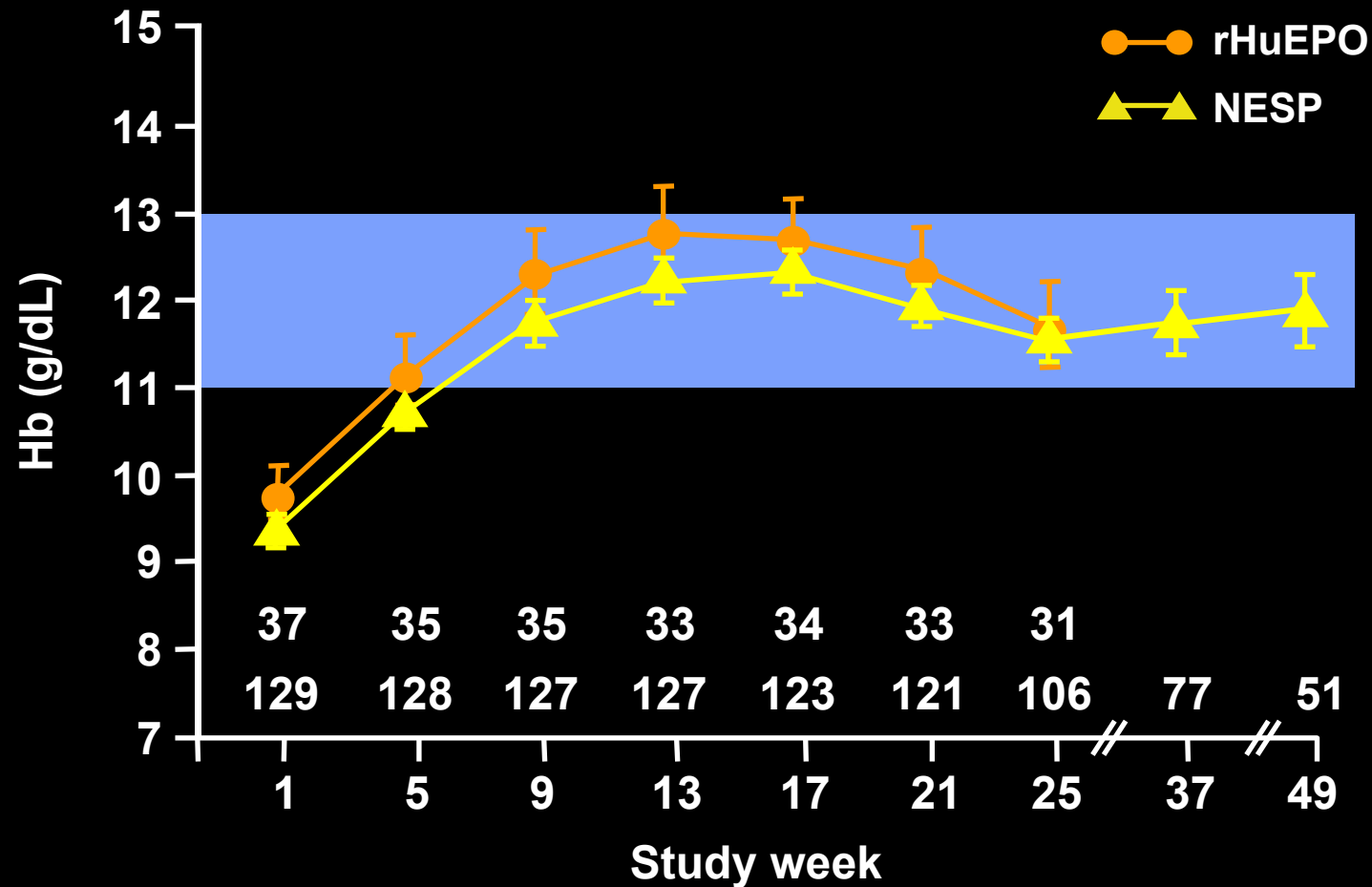
- Different mechanism of action
- Different molecular structure
- Increased biological activity



Biochemical and biological properties of rHuEPO and glycosylation analogs



Hb concentrations at 4-week intervals



Patient numbers:

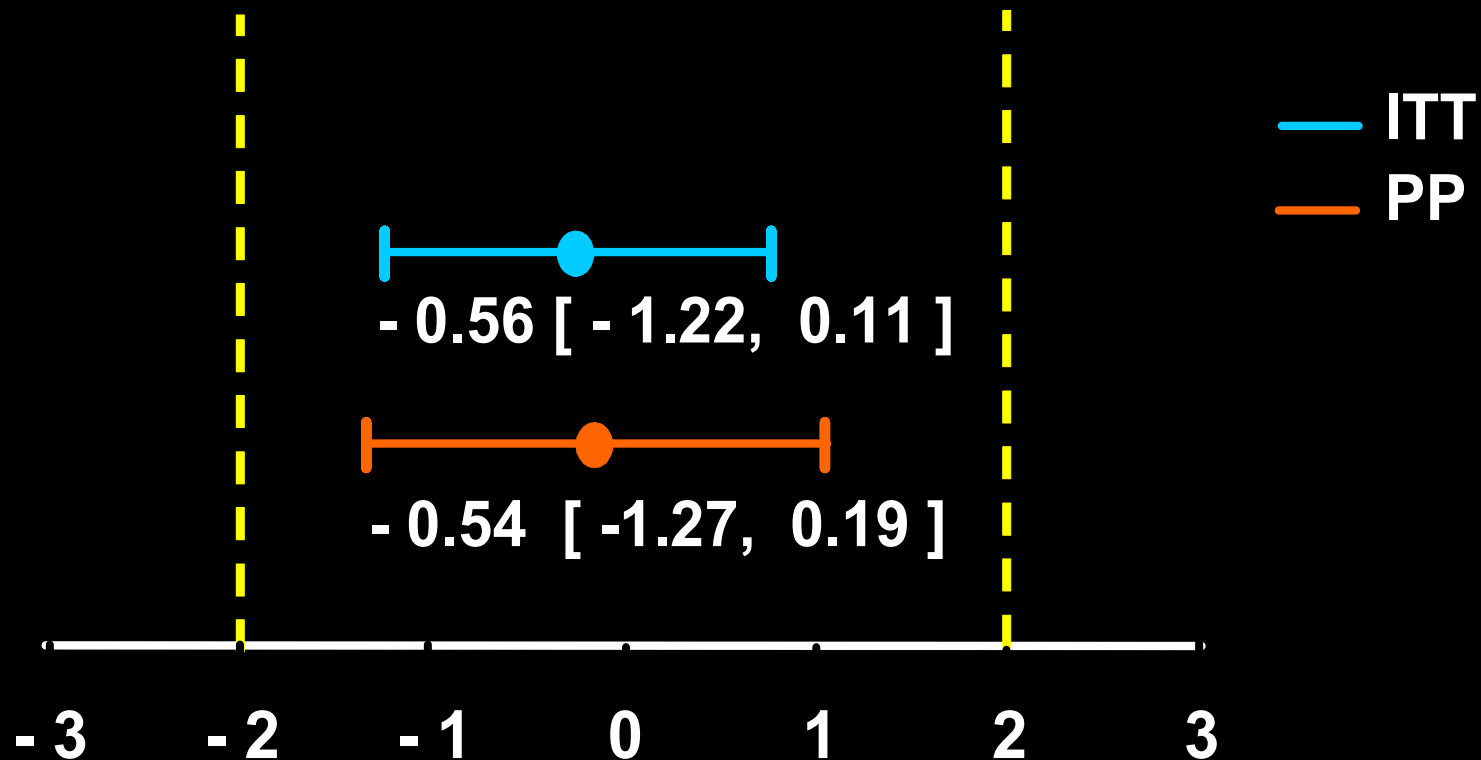
rHuEPO

NESP

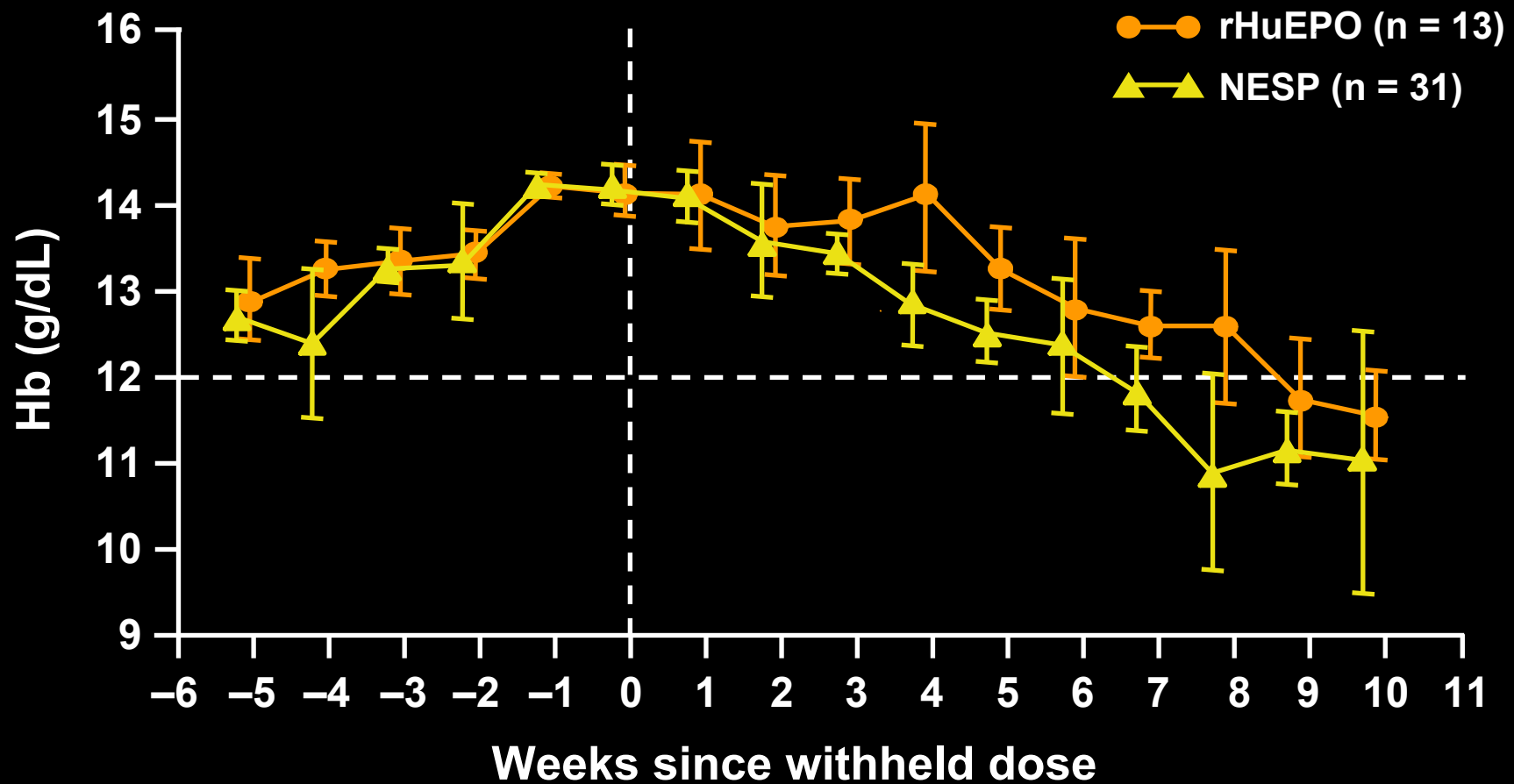
Once week epoetin beta in HD

Mean time-adjusted AUC for haematocrit

- Mean [90% CI]



Time for Hb to return to ≤ 12 g/dL after dose withheld due to Hb >14 g/dL



C.E.R.A.: pharmacodynamics, pharmacokinetics and efficacy in patients with chronic kidney disease

Francesco Locatelli[†] & Bruno Reigner

*[†]Direttore Struttura Complessa di Nefrologia e Dialisi, Azienda Ospedaliera di Lecco,
Ospedale Alessandro Manzoni, Via Dell' Eremo 9/11, 23900 Lecco, Italy*

**Expert
Opinion**

on Investigational Drugs 16 (10) 2007

Serum half life of ESAs

Agent	Population	Mean (\pm SE) half-life (h)	
		IV	SC
Epoetin alfa	Healthy volunteers ¹	6.8 \pm 0.6	19.4 \pm 2.5
Epoetin beta	Healthy volunteers ¹	8.8 \pm 0.5	24.2 \pm 2.6
Darbepoetin alfa	Peritoneal dialysis patients ²	25.3 \pm 2.2	48.8 \pm 5.2
C.E.R.A.	Healthy volunteers ³	133 \pm 9.8	137 \pm 21.9
	Peritoneal dialysis patients ⁴	134 \pm 19	139 \pm 20

1. Halstenson et al. *Clin Pharmacol Ther.* 1991;50:702-712

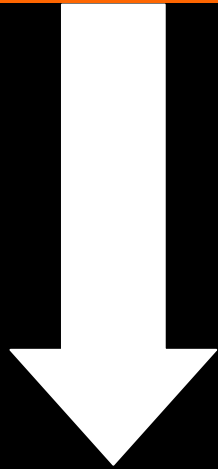
2. Macdougall et al. *J Am Soc Nephrol.* 1999;10:2392-2395

3. Dougherty et al. *ASCO* 2004

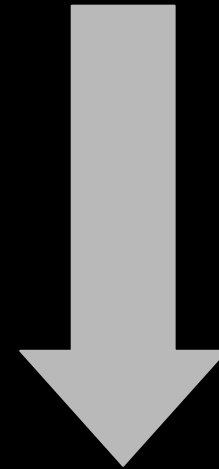
4. Macdougall et al. *ASN* 2005

Understanding how C.E.R.A. is different

**Receptor binding
properties**



**Pharmacokinetic
properties**



Different pharmacologic profile

CERA (Continuous Erythropoietin Receptor Activator) Maintains Hemoglobin Levels in Dialysis Patients when Administered Subcutaneously up to Once Every 4 Weeks

Francesco Locatelli¹, Giuseppe Villa², Manuel Arias³, Donatella Marchesi⁴, Frank C. Dougherty⁵, Ulrich Beyer⁵ on behalf of the BA16286 study group

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²Divisione de Nefrologia e Dialisi, Fondazione S. Maugeri, IRCCS, Pavia, Italy;

³Servicio de Nefrologia, Hospital Universitario Valdecilla, Santander, Spain;

⁴Unita Operativa di Nefrologia e Dialisi, Ospedali Riuniti di Bergamo, Bergamo, Italy;

⁵F. Hoffmann-La Roche, Basel, Switzerland

Presented at

American Society of Nephrology

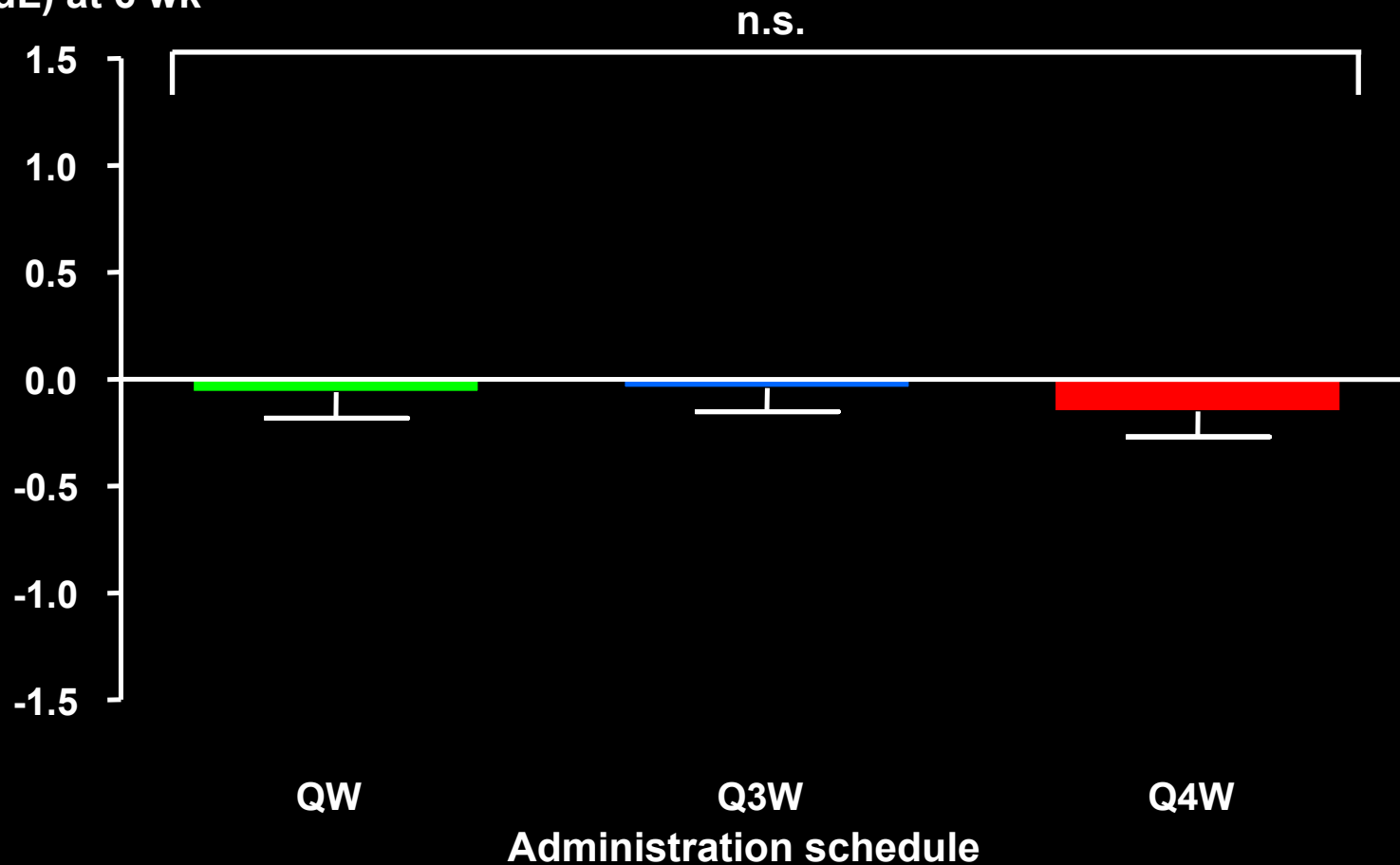
37th Annual Meeting

October 29 – November 1, 2004

C.E.R.A: Dose independent of schedule

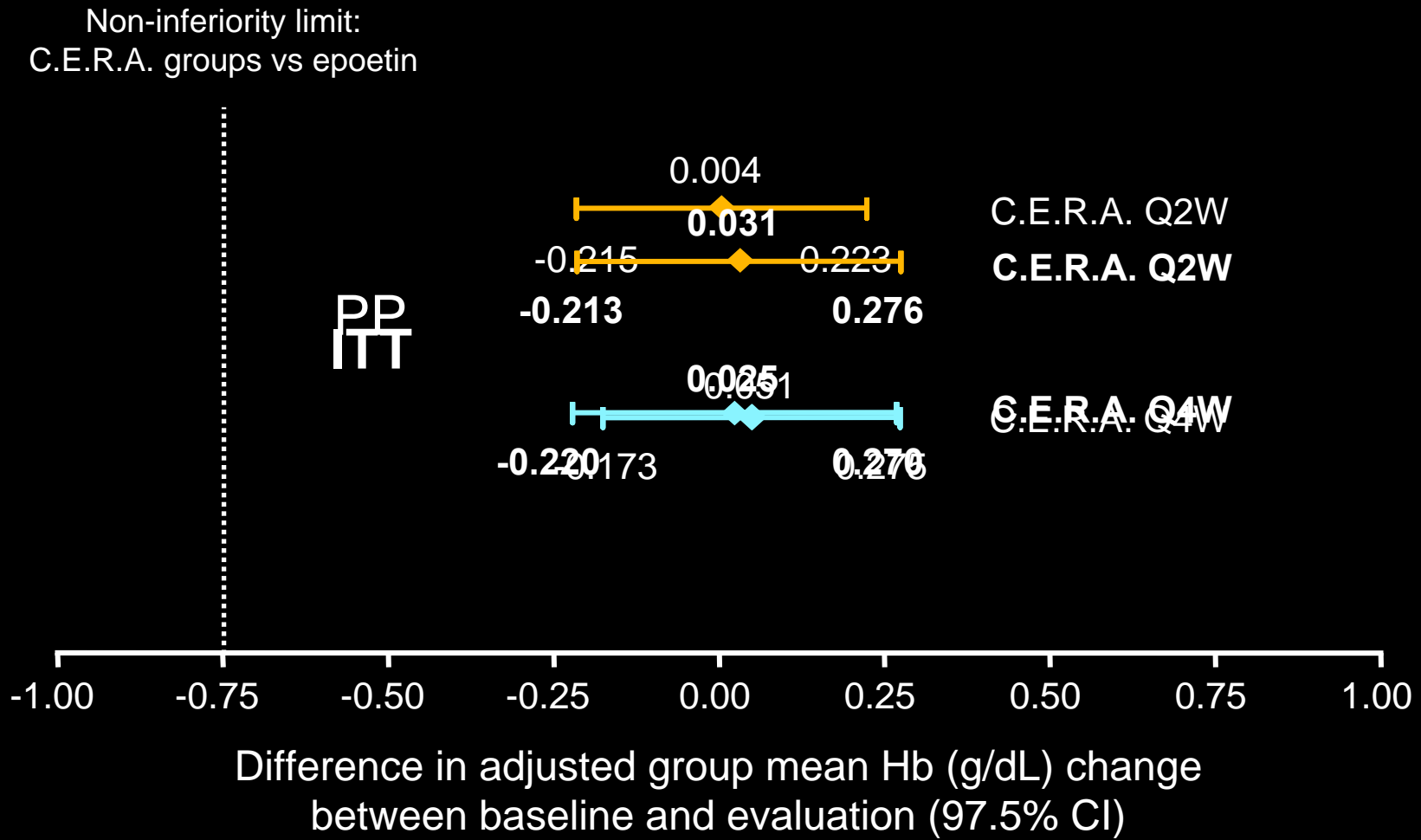
Core study, PP population, n=124 (BA16286)

Mean (SE) change
in Hb (g/dL) at 6 wk



Primary efficacy analysis

C.E.R.A. up to once-monthly as effective as epoetin TIW-QW

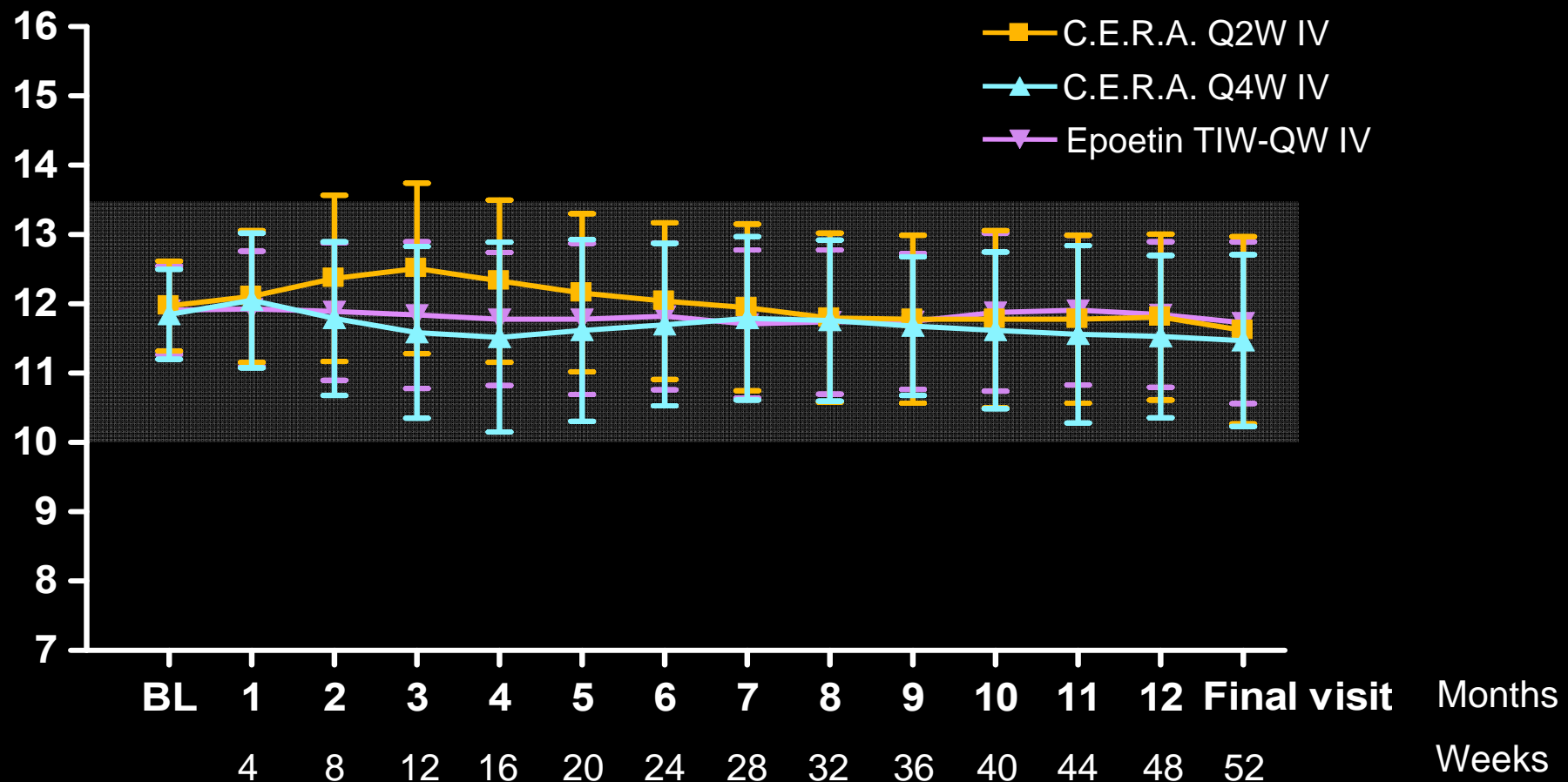


$P < 0.0001$ for all comparisons

Levin NW et al. *Lancet* 2007, 370 (9596): 1415-1421

IV C.E.R.A. once- and twice-monthly maintains stable Hb over one year

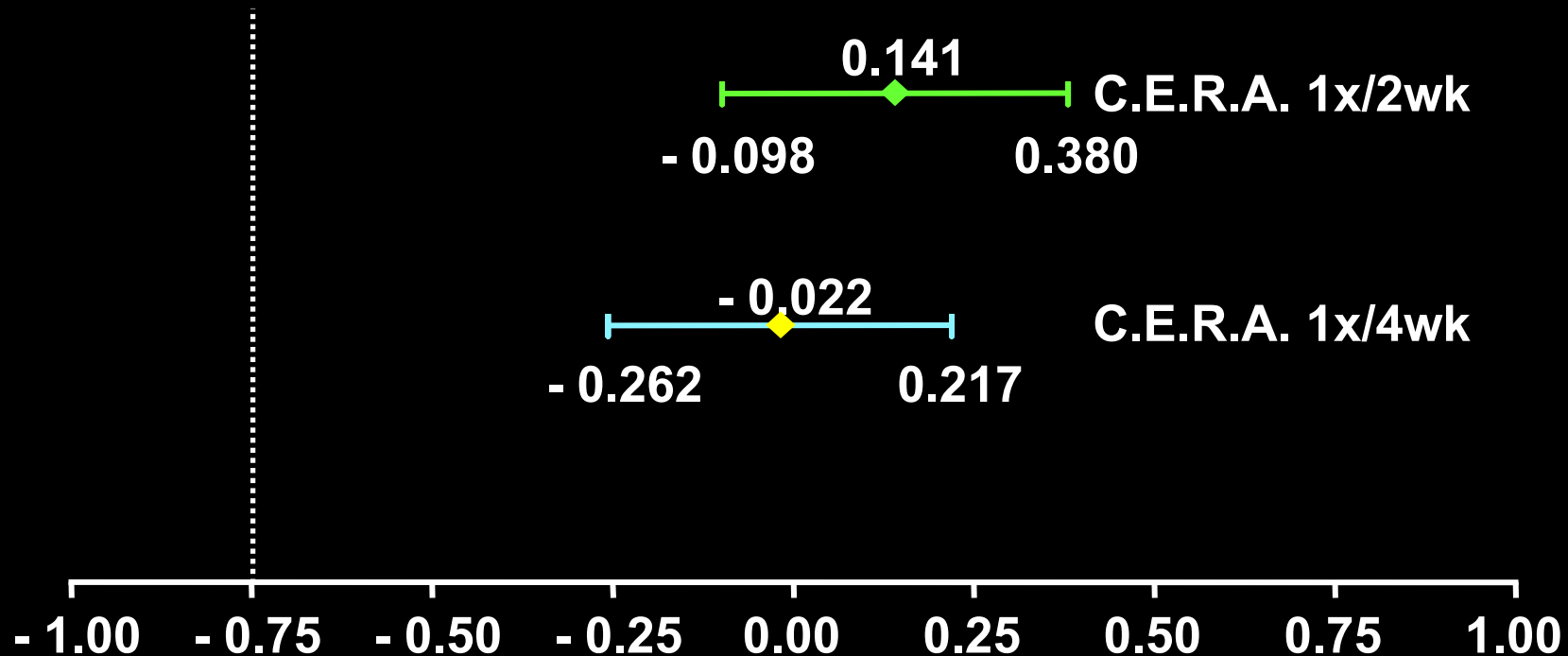
Mean (SD) Hb (g/dL)



SC C.E.R.A. once-monthly and twice-monthly as effective as epoetin 3x/wk

PROTOS: primary efficacy analysis (PP population)

Non-inferiority
lower 97.5% CI limit



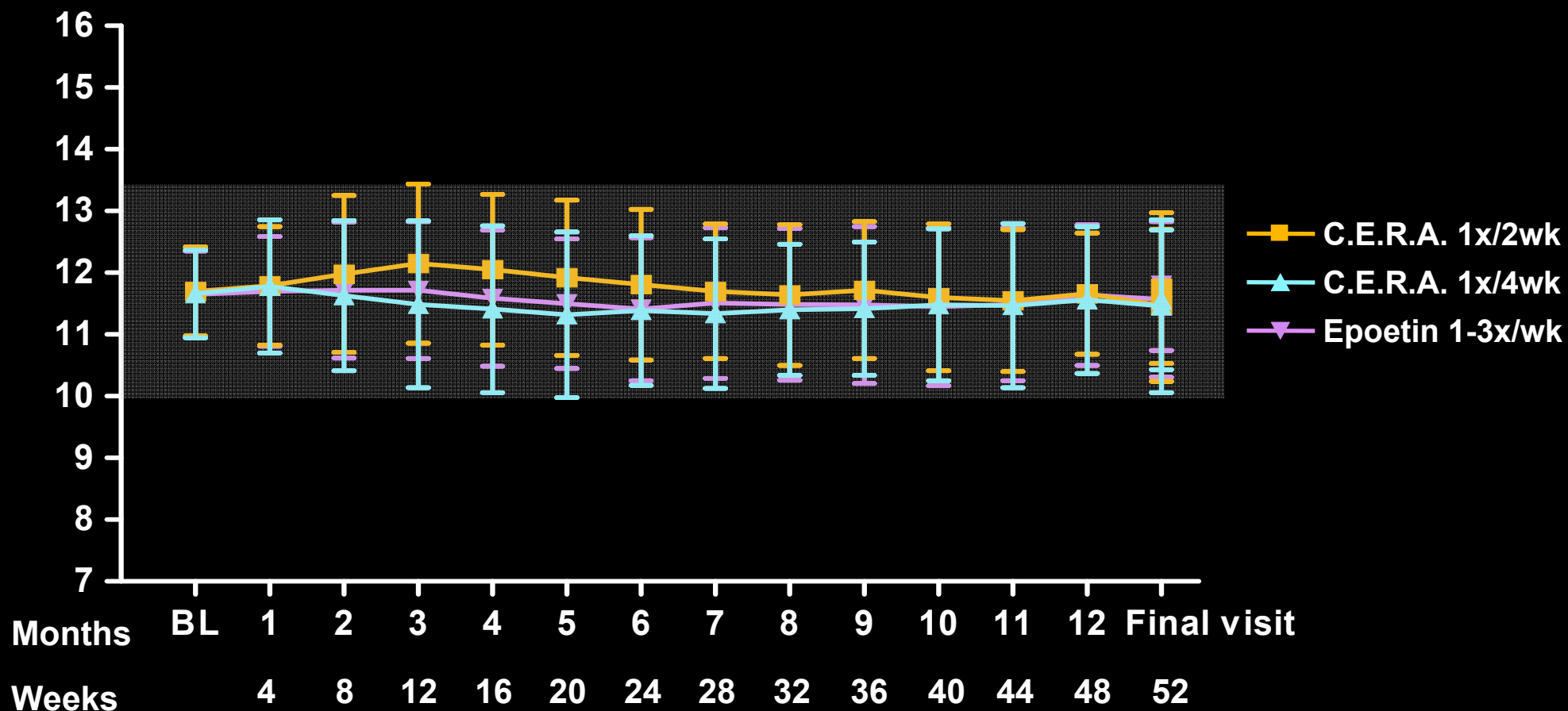
Difference in mean adjusted Hb versus epoetin (g/dL)

$P < 0.0001$ for all comparisons

Stable Hb maintenance with once-monthly SC C.E.R.A.

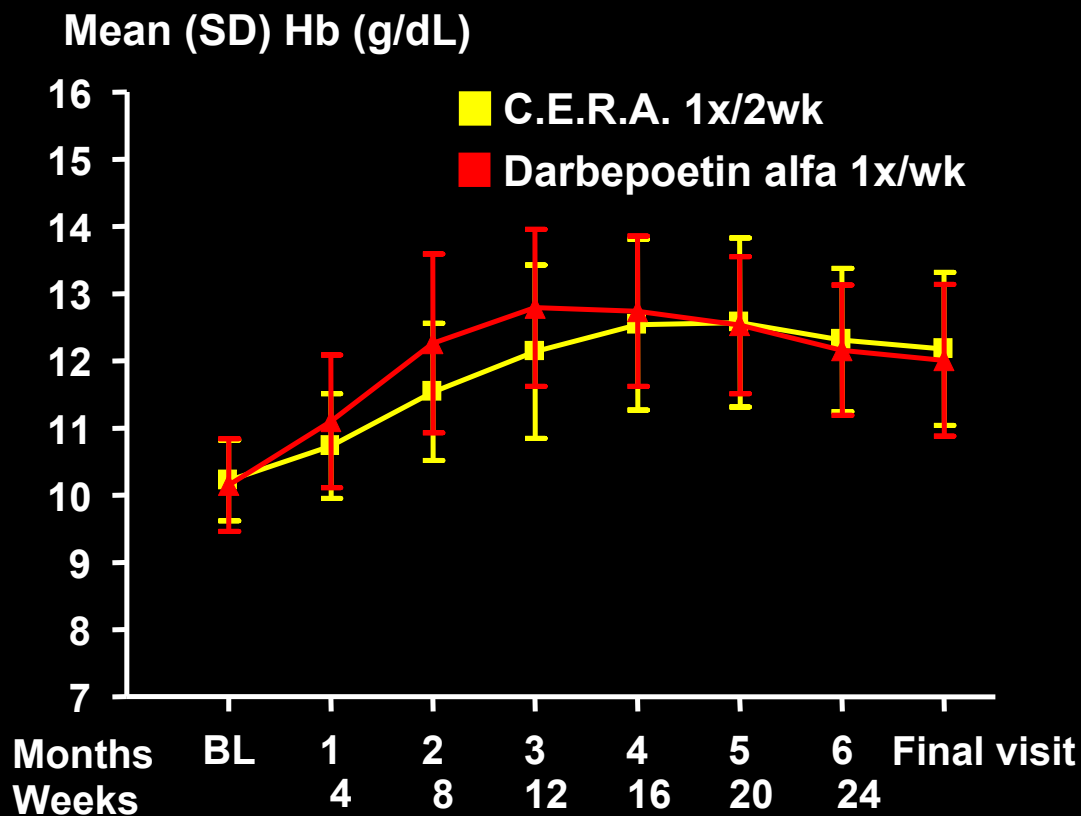
PROTOS: ITT population

Mean (SD) Hb (g/dL)



SC C.E.R.A.: Smooth and steady Hb increase with a high response rate

ARCTOS: ITT population



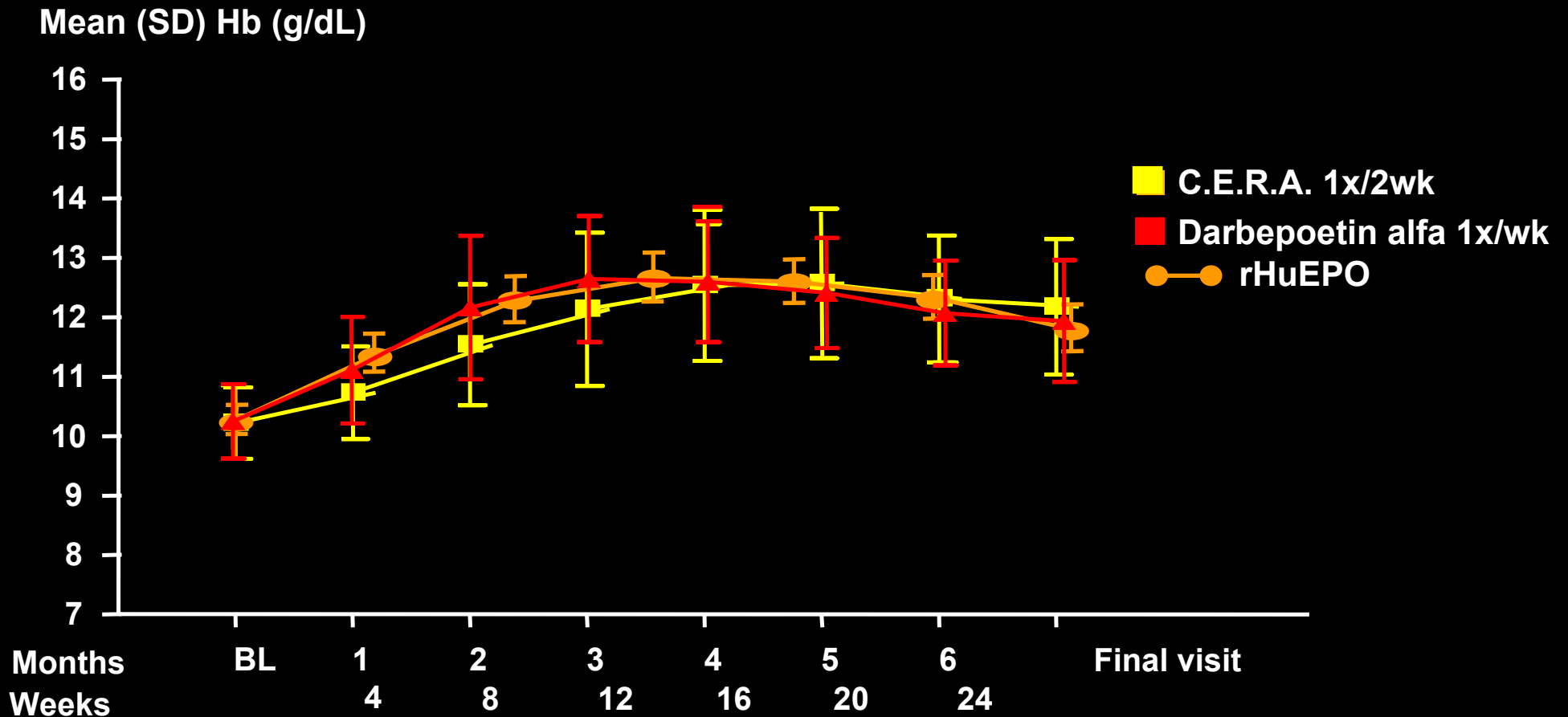
	Response rate (%)	95% CI
C.E.R.A. 1x/2wk	97.5	93.8-99.3
Darbepoetin alfa 1x/wk	96.3	92.1-98.6

Macdougall, ... Locatelli et al. Clin J Am Soc Nephrol. 2008 Mar;3(2):337-47

Hb concentrations during 24-week intervals

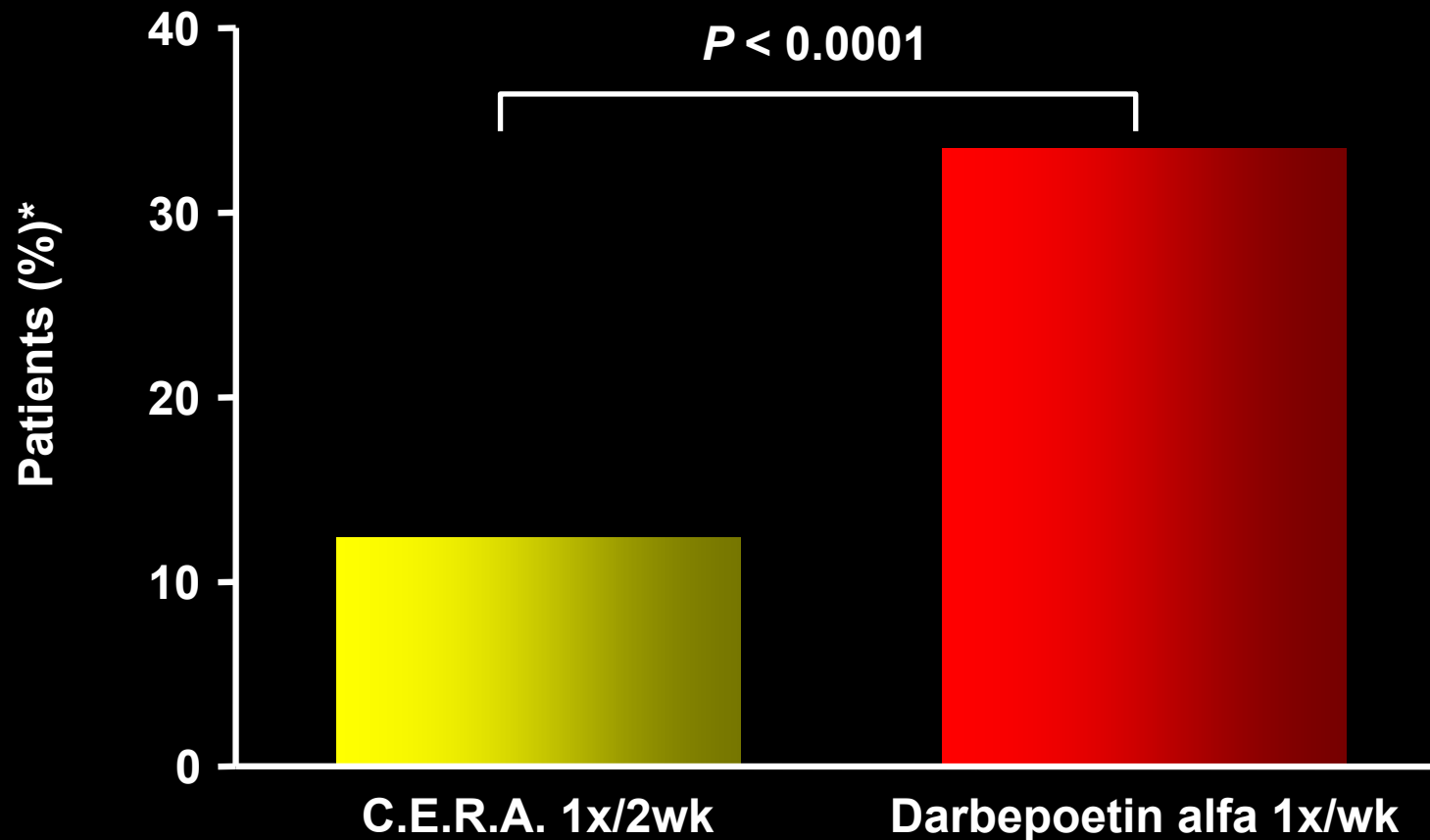
Locatelli F et al. *Kidney Int* 2001; 60: 741-747

Macdougall, ... Locatelli et al. *Clin J Am Soc Nephrol.* 2008 Mar;3(2):337-47



Fewer patients exceed Hb 13 g/dL with C.E.R.A. than with darbepoetin alfa

ARCTOS: ITT population

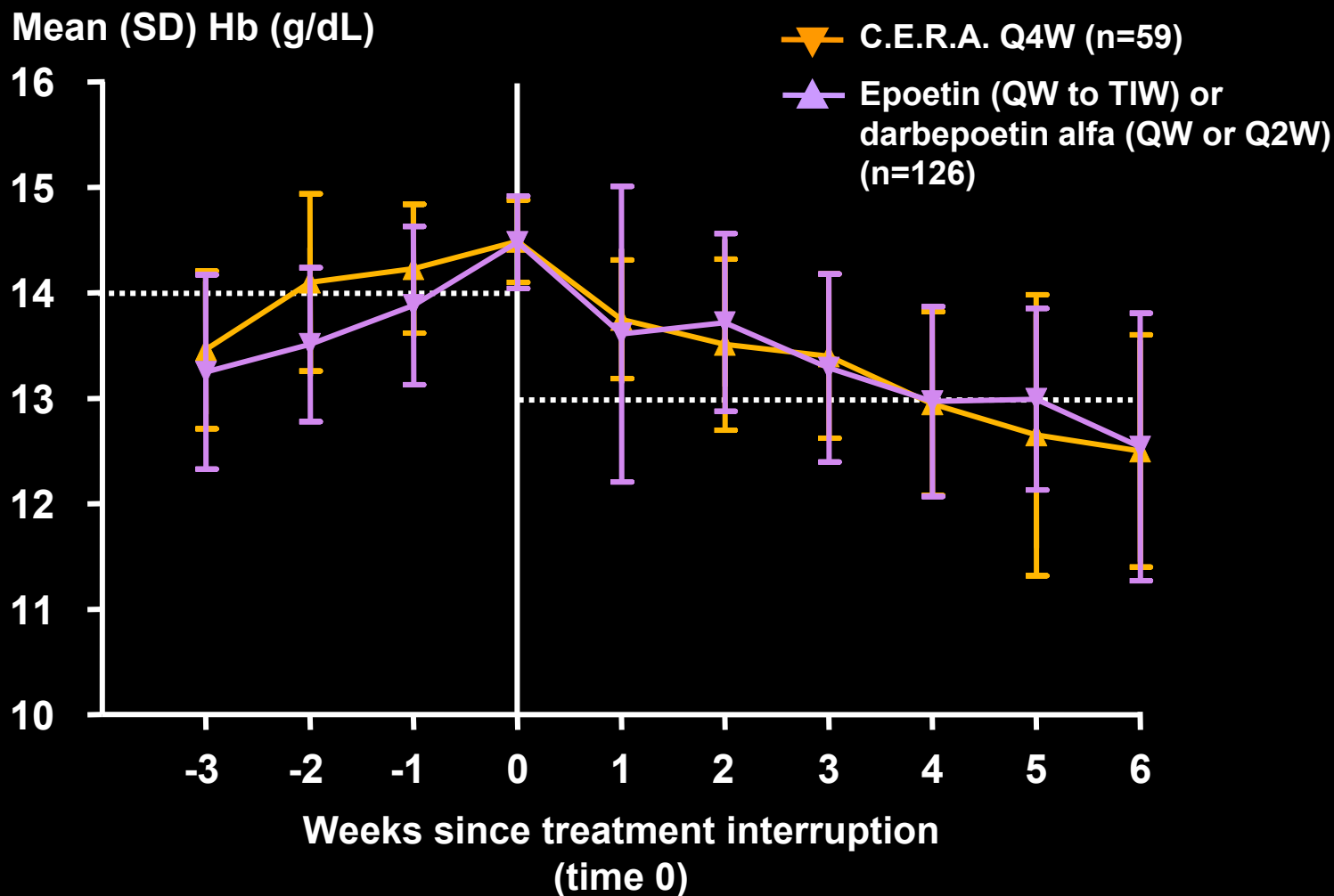


*Patients with ≥ 1 Hb value >13 g/dL during first 8 weeks

Macdougall, ... Locatelli et al. Clin J Am Soc Nephrol. 2008 Mar;3(2):337-47

Decline in Hb after withholding treatment

Long C.E.R.A. half-life does not affect Hb decline following dose interruption – pooled analysis of maintenance studies



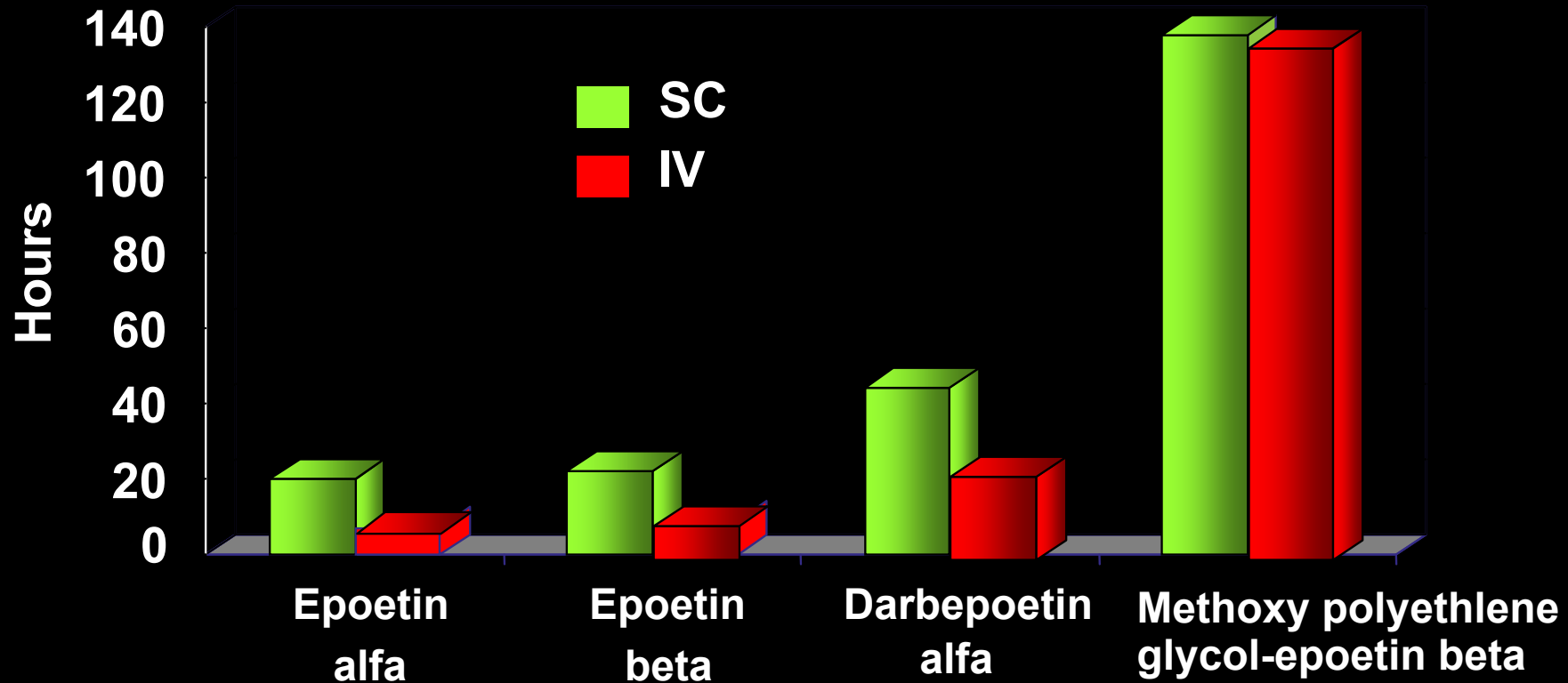
Safety populations

Half life comparison

Methoxy polyethylene glycol-epoetin beta's half-life is much longer than that of darbepoetin alfa

❖ 137 h vs 38 h when given SC

❖ 133 h vs 25 h when given IV



Halstenson. *Clin Pharmacol Ther.* 1991;50:702

Macdougall. *J Am Soc Nephrol.* 1999;10:23925

Reigner. *Nephrol Dial Transplant.* 2003;18(suppl 4):167 Abstract M527

Half life of epoetins

	$t_{1/2}$ (hours)	
	Intravenous	Subcutaneous
Epoetin alfa	6.8*	19.4*
Epoetin beta	8.8*	24.2*
Darbepoetin alfa †	25.3	48.8
Methoxy polyethylene glycol-epoetin beta	130	133
Hematide	75	~80

*Healthy volunteers

†Peritoneal dialysis patients

Halstenson. Clin Pharmacol Ther. 1991;50:702

Macdougall. J Am Soc Nephrol. 1999;10:2392

Reigner. Nephrol Dial Transplant. 2003;18(suppl 4):167. Abstract M527

Woodburn. Blood. 2004;104:2904

MIRACEL: study objectives

Primary objective

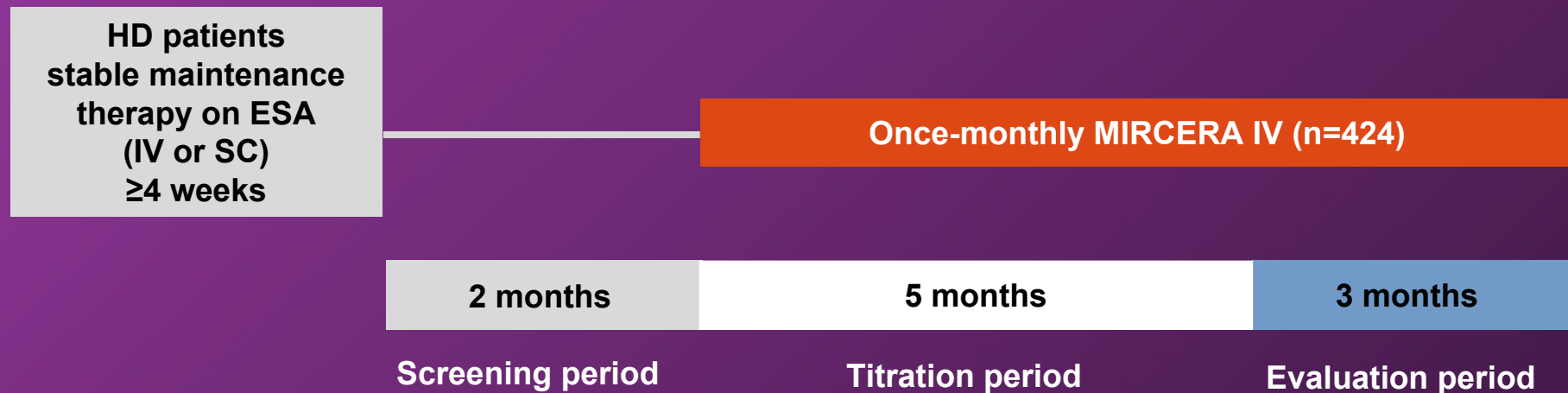
Investigate the efficacy of direct conversion of HD patients from shorter-acting ESAs to once-monthly MIRCERA

Secondary objective

Assess safety and tolerability of direct conversion to once-monthly MIRCERA

MIRACEL: study design

● Prospective, open-label, single-arm, multicentre study



● Primary end point

- No. patients maintaining Hb targets of 11-12.5 g/dL or 10-13 g/dL during the evaluation period

IV, intravenous; Hb, haemoglobin;
SC, subcutaneous

Fliser et al. *Curr Med Res Opin* 2010;26:1083-1089

MIRCERA dose conversion schedule

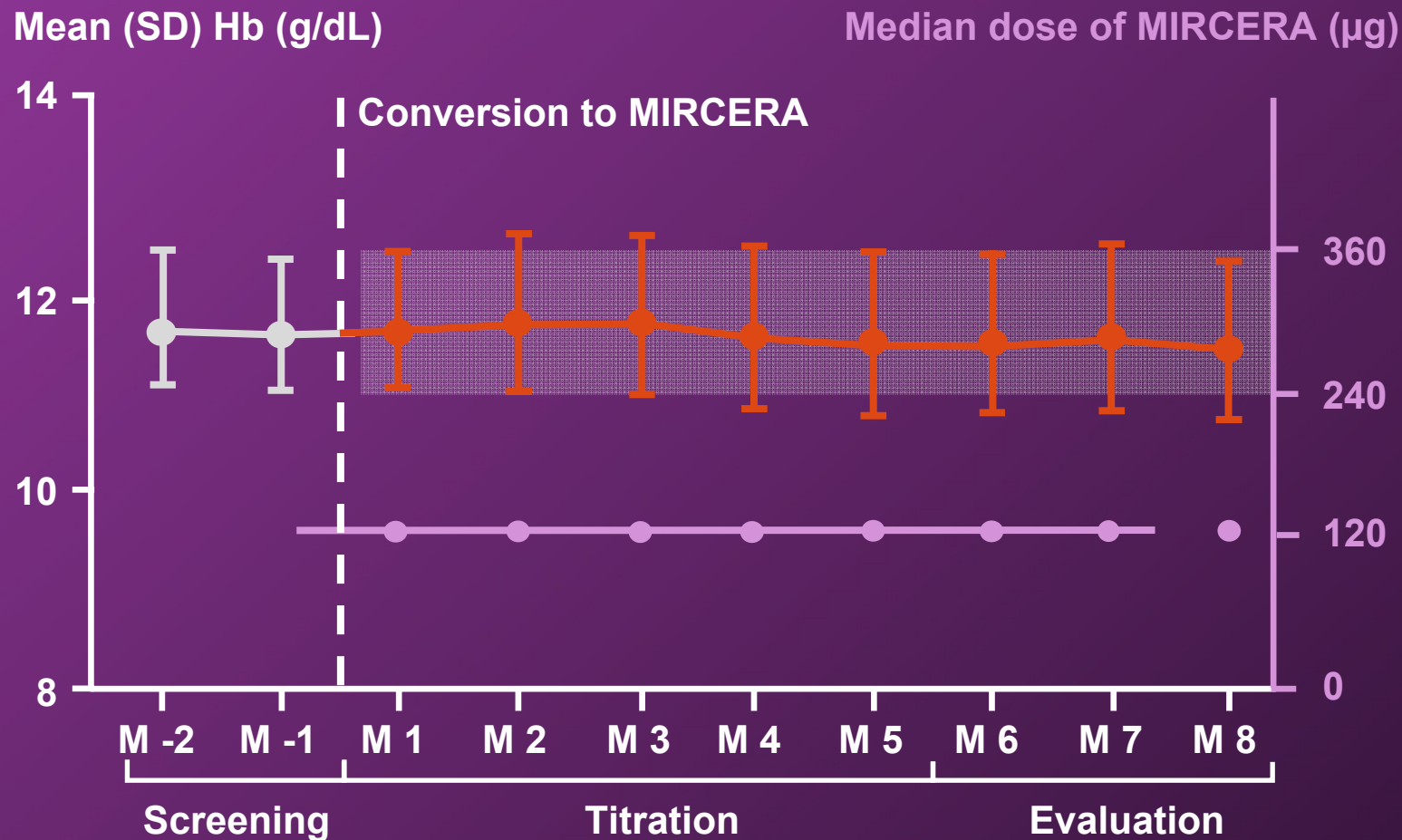
Previous ESA dose		MIRCERA
Epoetin weekly dose (IU)	Darbepoetin alfa weekly dose (μg)	MIRCERA once-monthly conversion dose (μg)
<8000	<40	125 ^a
8000-16000	40-80	200

^aAdministered 75 + 50 μg PFS;
Same dose for IV or SC administration

MIRACEL study: baseline patient characteristics

	Safety population (n=424)
Male, n (%)	258 (60.8)
Mean (SD) age, years	63.1 (14.7)
Mean (SD) Hb, g/dL	11.7 (0.84)
Diabetes mellitus, n (%)	90 (21.2)
Hypertension, n (%)	311 (73.3)
Mean (SD) time on dialysis, years	4.3 (4.3)
Previous ESA treatment, n (%)	
Epoetin alfa	113 (26.7)
Epoetin beta	188 (44.3)
Epoetin delta	5 (1.2)
Darbepoetin alfa	118 (27.8)
Previous route of ESA administration, n (%)	
IV	336 (79.2)
SC	88 (20.8)

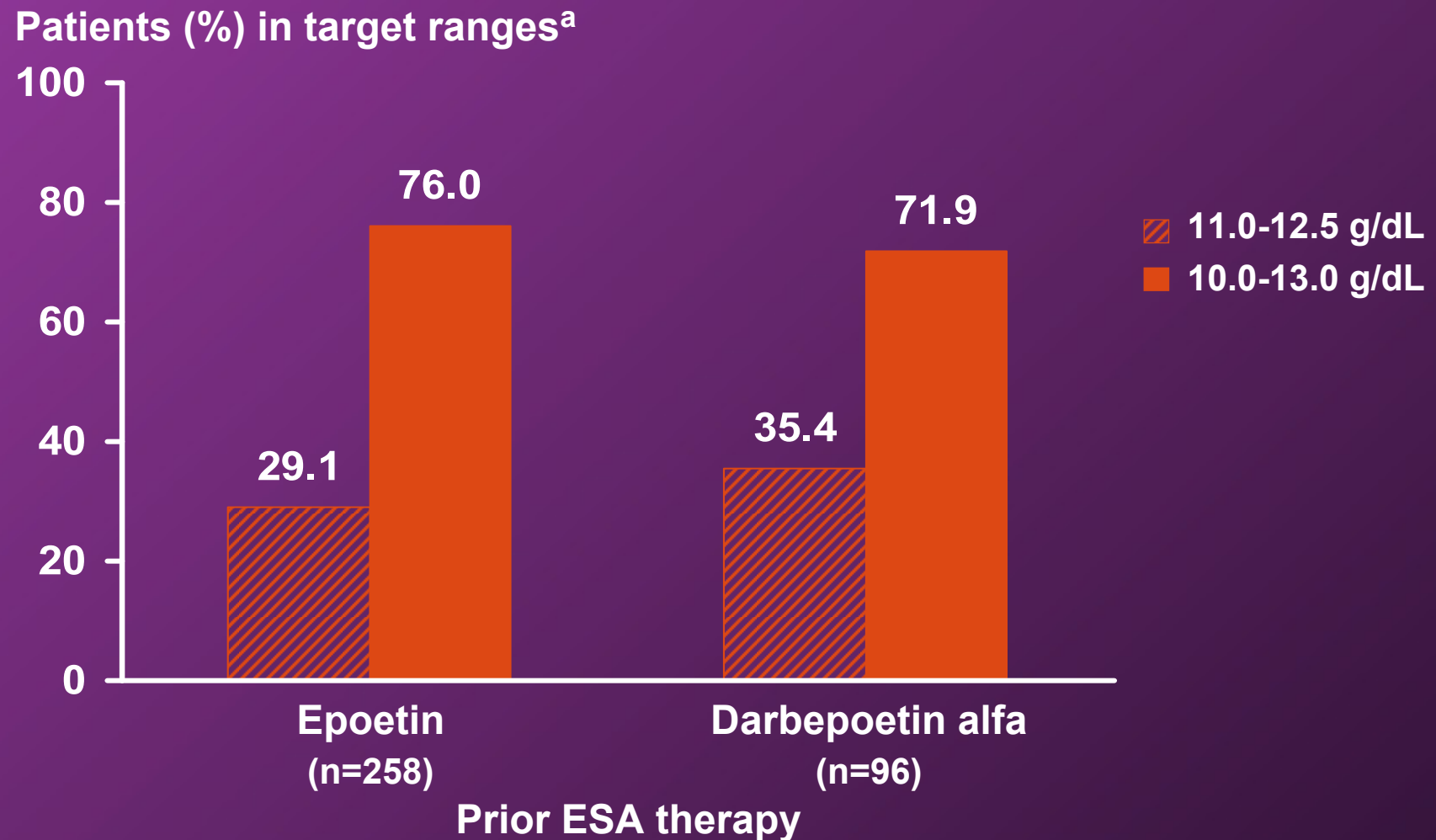
Direct conversion to once-monthly MIRCERA maintains stable Hb levels with consistent dosing



ITT population (n=416)

Fliser et al. *Curr Med Res Opin* 2010;26:1083-1089

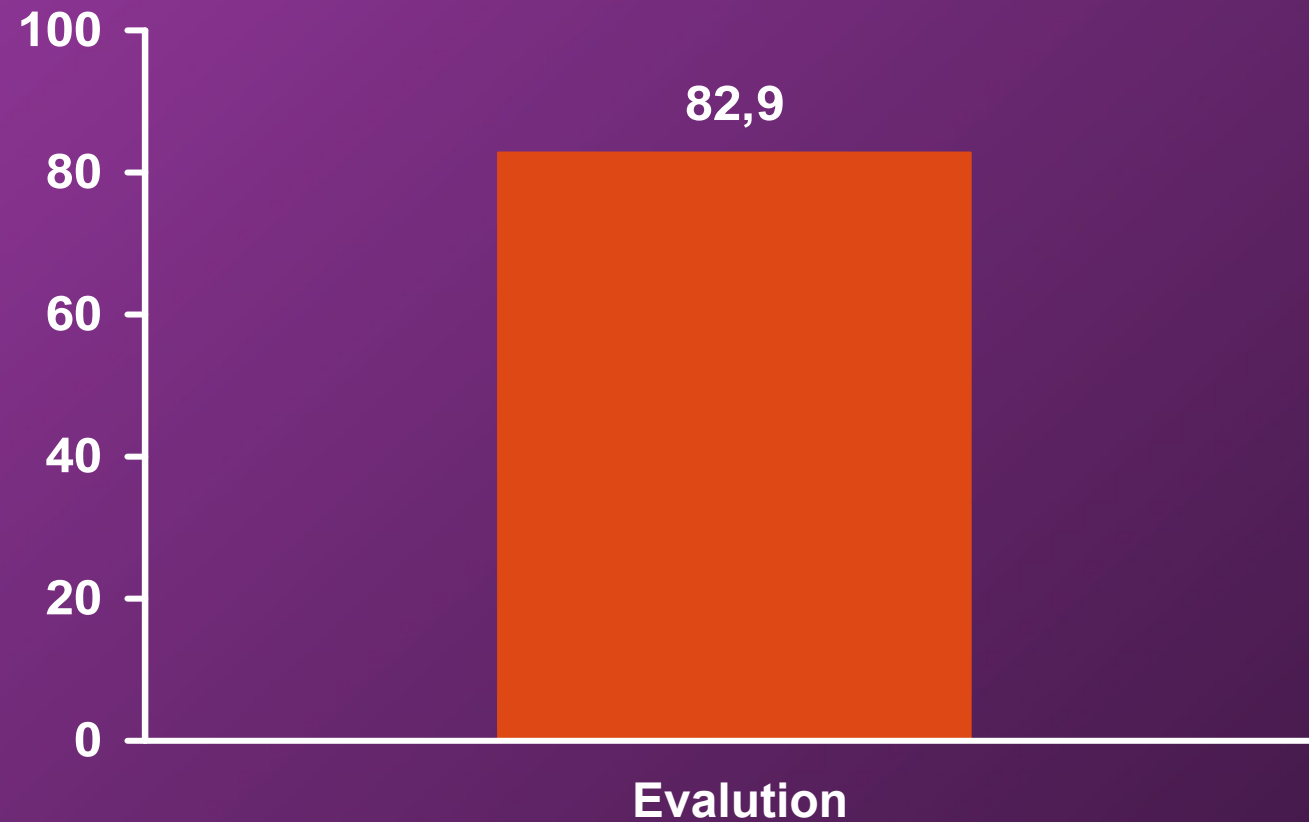
Patients maintained Hb targets during evaluation regardless of previous ESA therapy



^aResponders ITT population (n=354)

Patients maintained Hb levels during evaluation periods

Patients (%) exhibited ≤ 1 g/dL change from phase specific individual means



No more than 2 dose changes in 90% of the population during the titration period

MIRCERA dose changes	ITT population (n=416)
Any change	
Mean \pm SD	2.0 \pm 1.4
Median (range)	2 (0-5)
Any dose decrease, mean \pm SD	0.93 \pm 1.0
Any dose increase, mean \pm SD	1.1 \pm 1.0
≥ 1 dose change	351 (84.4%)

C.E.R.A. safety profile: a pooled analysis in patients with chronic kidney disease

F. Locatelli¹, J.F.E. Mann², J.-C. Aldigier³, D. Sanz Guajardo⁴, R. Schmidt⁵,
B. Van Vlem⁶, W. Sulowicz⁷, F. C. Dougherty⁸ and U. Beyer⁸

¹*Department of Nephrology and Dialysis and Renal Transplant, A. Manzoni Hospital, Lecco, Italy,* ²*KFH Kidney Center, Munich, Germany,* ³*Néphrologie-Hémodialyse Hôpital Dupuytren, Limoges, France,* ⁴*University Hospital Puerta de Hierro Majadahonda, Madrid, Spain,* ⁵*West Virginia University School of Medicine, Morgantown, WV, USA,* ⁶*Department of Nephrology, Dialysis and Hypertension, O.L. Vrouw Ziekenhuis, Aalst, Belgium,* ⁷*Department of Nephrology, Collegium Medicum Jagiellonian University, Cracow, Poland, and* ⁸*F. Hoffmann-La Roche Ltd., Basel, Switzerland*

Conclusion

- Direct conversion from shorter-acting ESAs to once-monthly MIRCERA is easily achieved
- 82.9% of patients exhibited ≤ 1 g/dL change from phase specific individual means during evaluation period
- No more than 2 dose changes in 90% of the population during the titration period to maintain Hb levels in target range
- MIRCERA was well tolerated
- Once-monthly MIRCERA simplifies anaemia management by reducing:
 - staffing time for tasks related to ESA administration
 - the potential for dosing errors