

# **Peginesatide Injection**

For the Treatment of Anemia in CKD  
Patients on Dialysis

**Oncologic Drugs Advisory Committee**

December 7, 2011

**Affymax, Inc.**

# Introduction

## **Christine Conroy, PharmD**

Vice President, Regulatory Affairs

Affymax, Inc.

# Drug Class and Proposed Indication

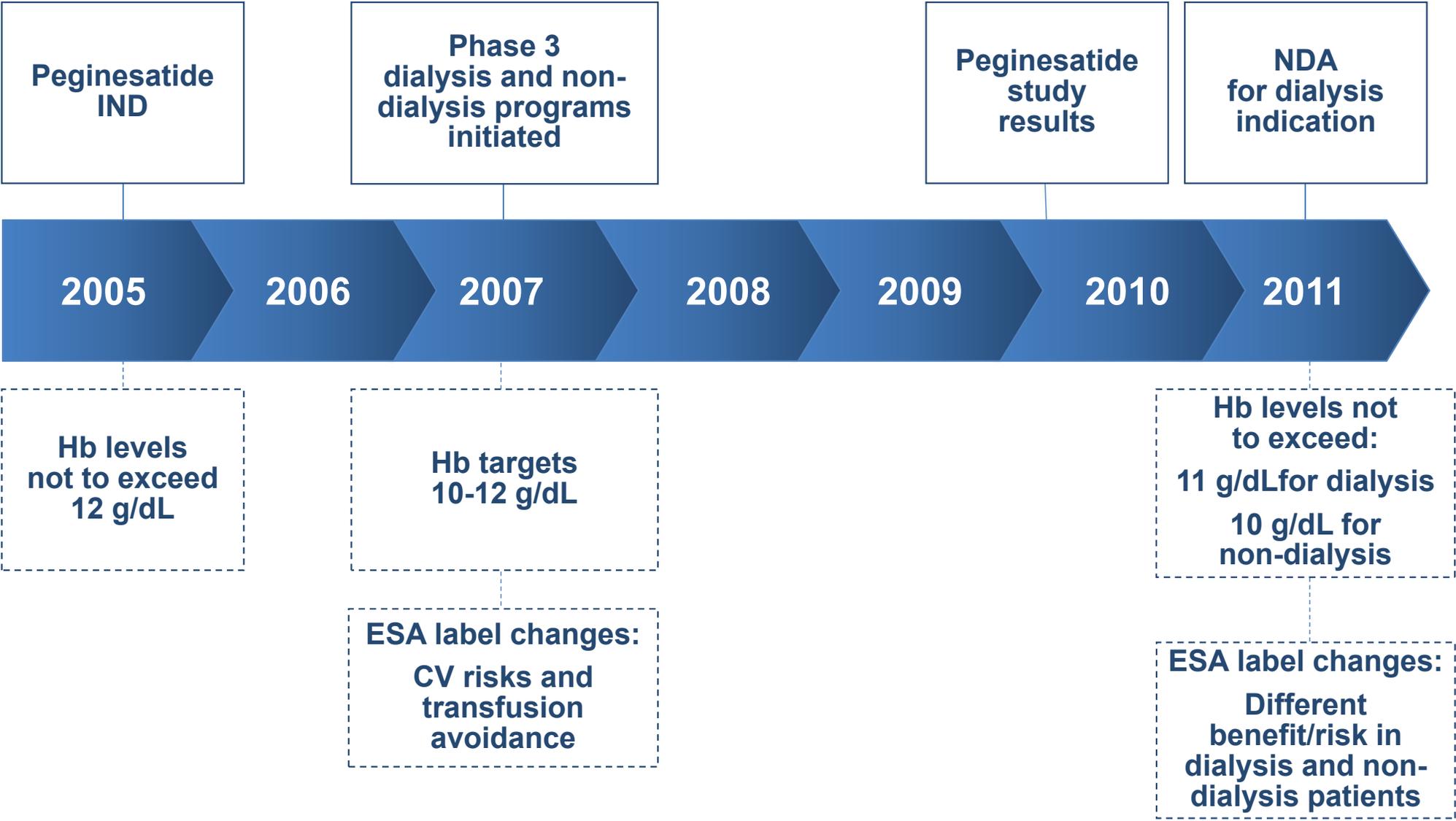
- **Peginesatide is an erythropoiesis stimulating agent (ESA)**
- **Proposed indication is for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis**

# **Peginesatide:**

## **An ESA with Once Monthly Dosing**

- **Synthetic, dimeric peptide**
- **Binds to and activates the erythropoietin (EPO) receptor like other ESAs**
- **Treatment goal is to manage anemia and avoid transfusions**
- **No structural homology and no shared epitopes with native EPO or recombinant ESAs**
- **PEGylation permits once monthly dosing**

# Regulatory History of Peginesatide and ESAs in Chronic Kidney Disease



# Criteria to be Considered for Approval

- **Phase 3 program results demonstrate that peginesatide is:**
  - Not importantly inferior to comparators for efficacy
  - Not importantly inferior to comparators for safety, with emphasis on cardiovascular safety
- **Evaluate Dialysis and Non-Dialysis populations separately**

# Concurrent Phase 3 Programs in Dialysis and Non-Dialysis

**Dialysis Program  
Study 12 & Study 14**

**Non-Dialysis Program  
Study 11 & Study 13**

- **Efficacy: non-inferiority in each study**
- **Blinded, independently adjudicated CV safety**
- **Pre-specified CV safety analyses:**
  - Pooled across 2 programs
  - Within each program (dialysis and non-dialysis)
- **Data support use in dialysis patients**

# Peginesatide Presentation Highlights

- **Comprehensive dialysis program stands alone**
  - Safety and efficacy data consistent within and between two well-controlled studies
  - Extensive evaluation of CV safety data in dialysis and non-dialysis support use in dialysis
- **Different benefit-risk profiles in dialysis and non-dialysis populations**
- **Availability would provide a new option in a setting where there are few alternatives**

# Agenda

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**Introduction**

**Christine Conroy, PharmD**  
Affymax, Inc.

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**Anemia of Chronic Kidney Disease**

**Anatole Besarab, MD**  
Henry Ford Hospital

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**Efficacy and Safety of Peginesatide**

**Anne-Marie Duliege, MD**  
Affymax, Inc.

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**Risk Benefit Summary**

**Krishna Polu, MD**  
Affymax, Inc.

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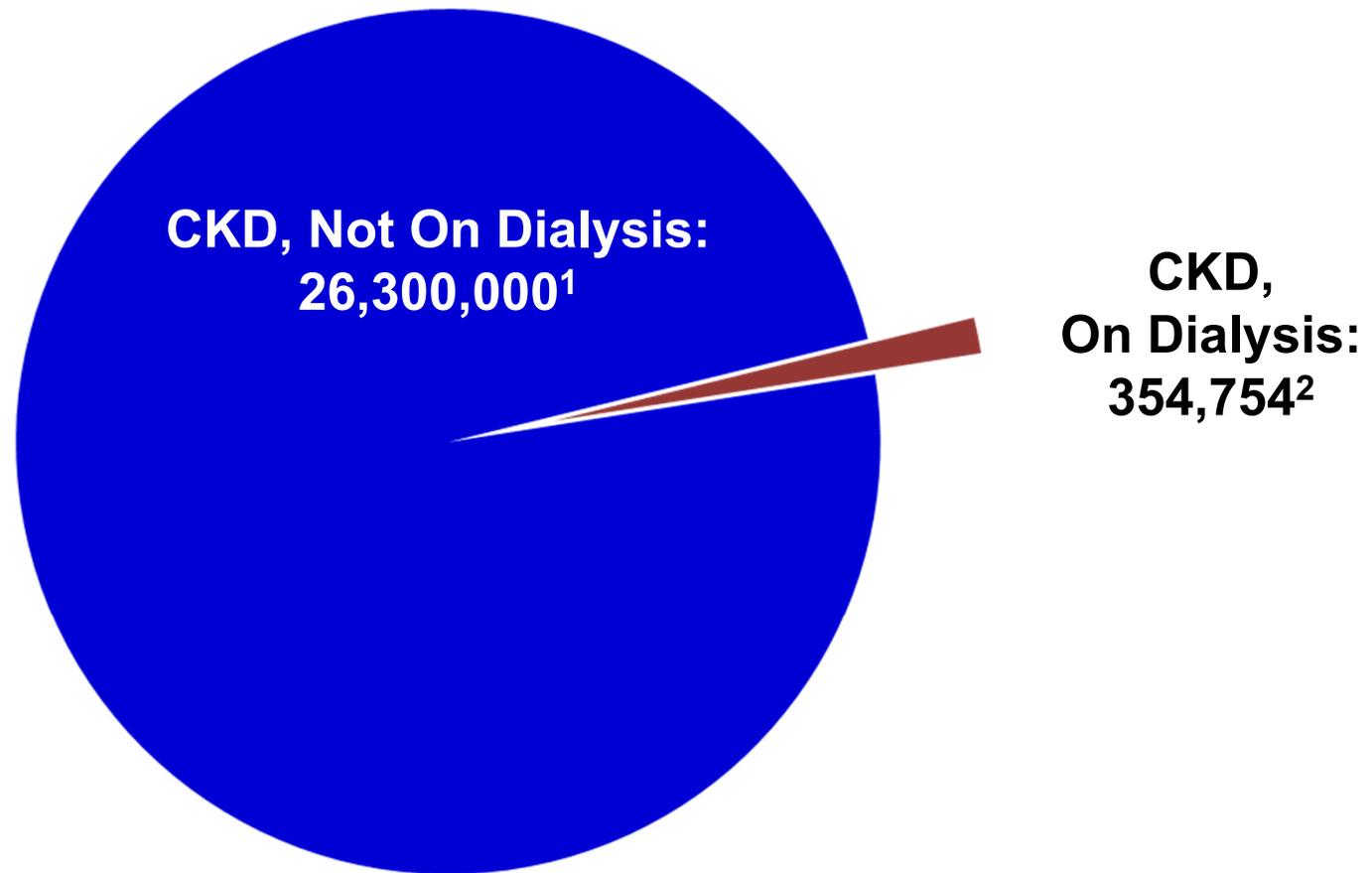
# Anemia of Chronic Kidney Disease (CKD)

## **Anatole Besarab, MD**

Director of Clinical Research  
Section of Nephrology and Hypertension  
Henry Ford Hospital

Clinical Professor, Wayne State University  
Detroit, MI

# Prevalence of Chronic Kidney Disease

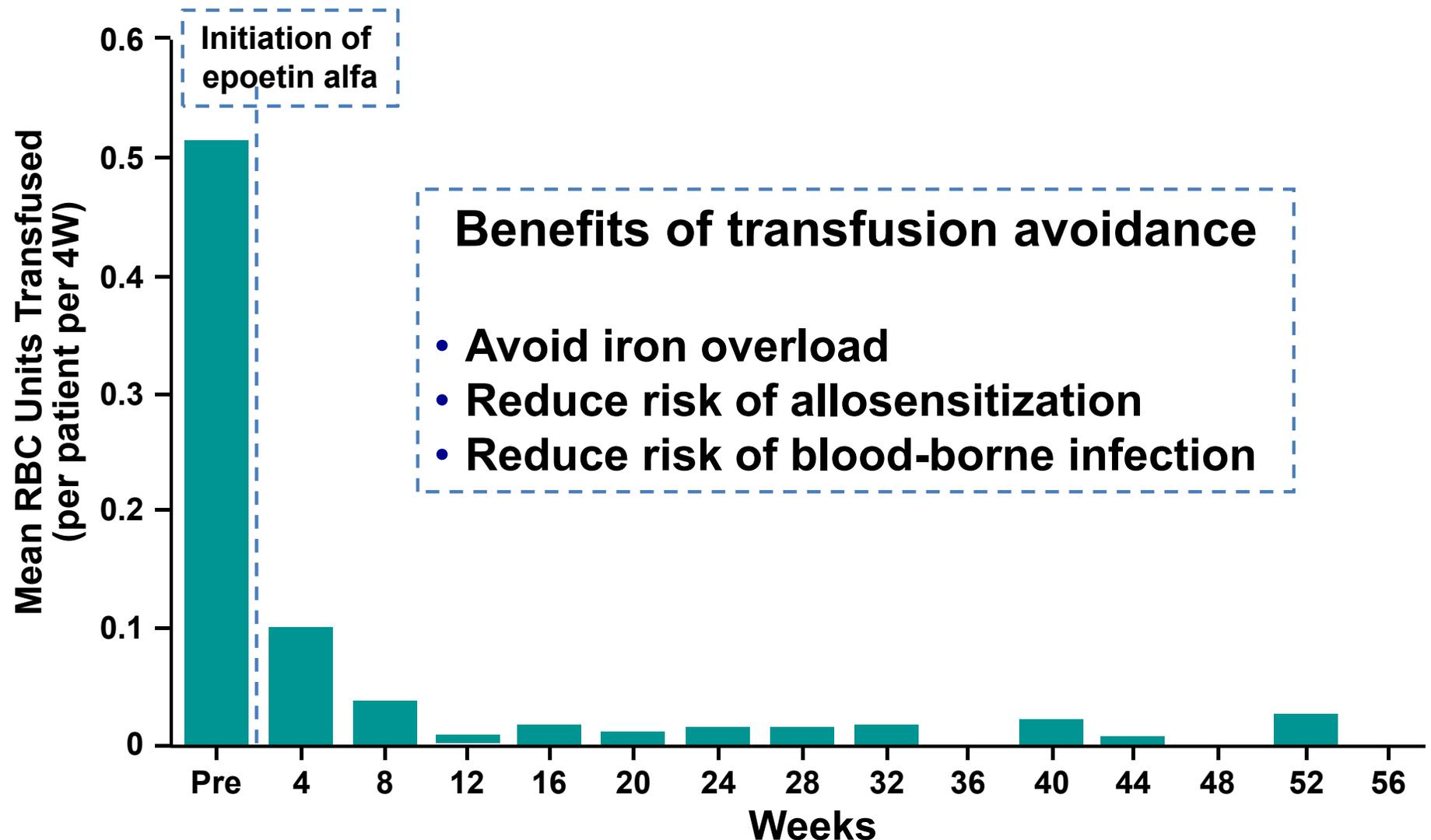


1. Coresh *JAMA* 2007.
2. USRDS (2008 data).

# Anemia in Dialysis Patients

- **Dialysis patients suffer from multiple comorbidities**
  - Severe anemia
  - Metabolic bone syndrome
  - Cardiovascular disease
  - Diabetes
- **Prior to ESAs**
  - Highly symptomatic
  - Therapeutic options inadequate
  - Transfusion-dependence

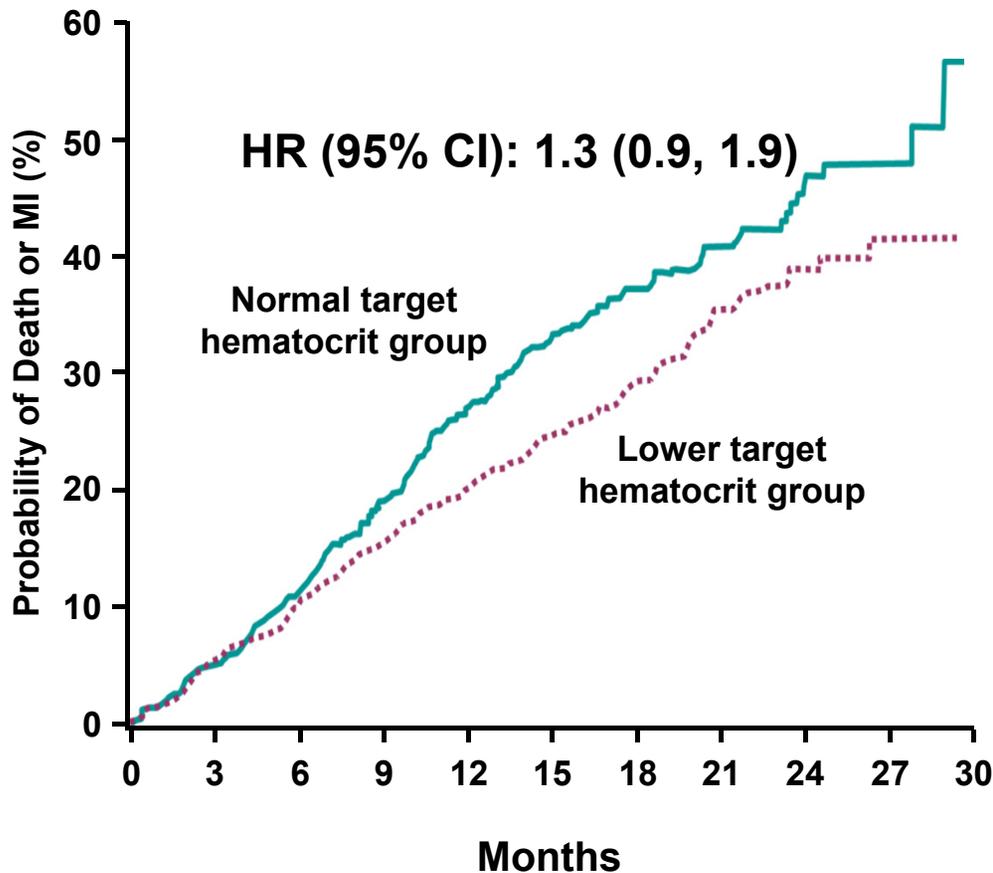
# Dialysis: Clinical Benefit of Transfusion Avoidance With ESAs



Eschbach JW, et al. *Annals of Internal Medicine*, 1989.  
Ibrahim. *Clinical Transplantation*, 2011.

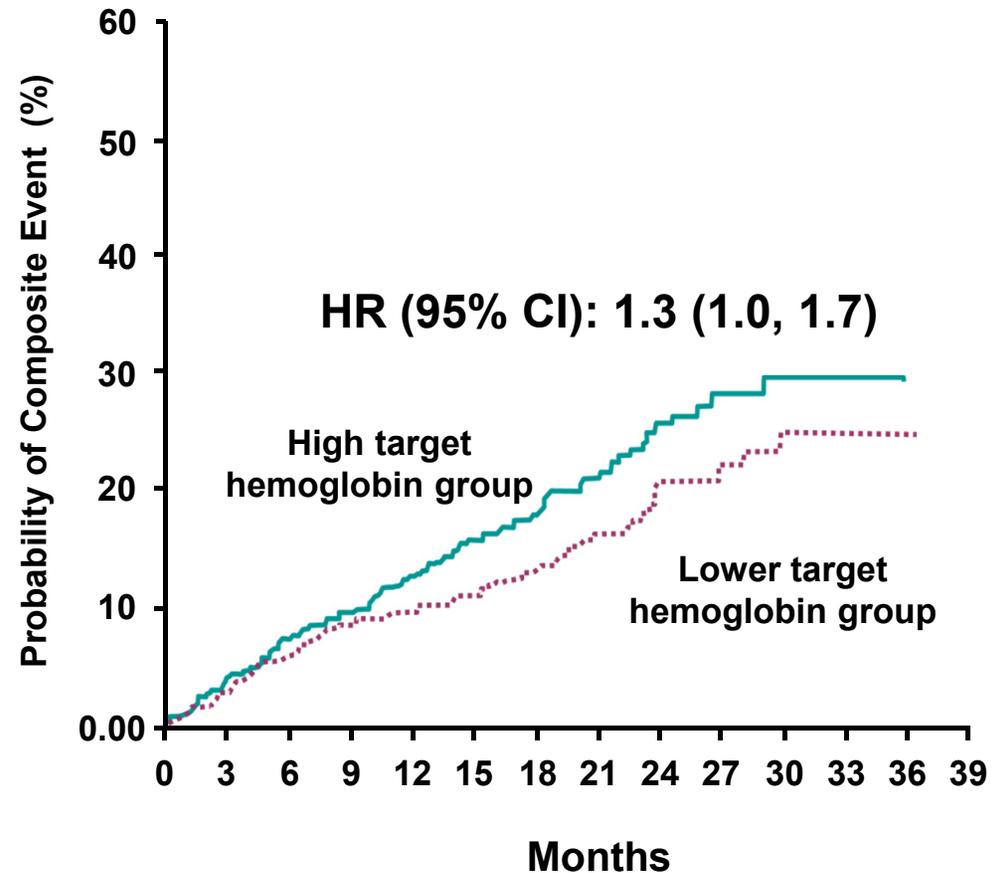
# No CV Benefit with Targeting Higher Hb

**Normal Hematocrit Study:  
(Dialysis)**



Besarab A, et al. *NEJM*. 1998.

**CHOIR Study:  
(CKD, not on dialysis)**



Singh A, et al. *NEJM*. 2006.

# TREAT Study: Limited Role of ESAs in Non-Dialysis CKD

## Study design

- ~4000 Type II diabetics with CKD not on dialysis
- Darbepoetin targeted to a Hb of 13 g/dL vs placebo with rescue
- CV outcomes

## Findings

- **No clear benefit**
  - No CV risk reduction
  - Two-fold higher risk of stroke in darbepoetin arm
- **Approximately 75% of placebo subjects did not require chronic ESA to avoid transfusion**

# Physiologic Differences Between Non-Dialysis and Dialysis Populations

Non-Dialysis	Dialysis
Wide range of renal function (GFR: 5-120 mL/min)	All lack renal function (GFR: <5 mL/min)
No anemia -> moderate anemia	Severe anemia
Development of heart disease <u>Risk factors:</u> <ul style="list-style-type: none"> <li>• Traditional</li> <li>• Non-traditional (eg, GFR)</li> </ul>	Progression of heart disease → CHF
	Dialysis procedure-related derangements <ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Volume overload, pulmonary edema</li> <li>• Electrolyte fluxes, arrhythmias</li> </ul>
Two populations have different treatment responses (eg, statins, coronary stents)	

Baigent and Landry. *Kidney Int*, 2003; Baigent et al. *Lancet*, 2011; Tsai. *JACC*, 2011.  
Kalantar-Zadeh. *HTN*, 2005

# Role of ESAs: Dialysis vs Non-Dialysis

## Non-Dialysis

**Less transfusion-dependent**

**Moderate usually  
asymptomatic anemia**

**ESA labeling: As needed**

**Limited Role for ESA**

## Dialysis

**Transfusion-dependent**

**Severe  
symptomatic anemia**

**ESA labeling: Chronic use**

**Clear Role for ESA**

# Medical Need - Peginesatide

- **Maintenance of hemoglobin**
- **Transfusion avoidance**
- **Once monthly dosing advantages**
  - Simplify anemia management
  - Reduced number of injections
  - Patients who self-inject
    - Home HD and peritoneal dialysis
- **Potential option for patients with pure-red cell aplasia (PRCA)**

# Conclusions

- **Patients on dialysis benefit from ESA therapy**
- **Non-dialysis and dialysis patients are different**
- **Additional treatment options are needed**
- **Long-acting ESAs could provide options that allow better care for this ill population**

# Efficacy and Safety of Peginesatide

**Anne-Marie Duliege, MD**

Chief Medical Officer, Affymax

# Efficacy Presentation

- **Program objectives**
- **Peginesatide pharmacology**
- **Clinical development program**
- **Efficacy and dosing in dialysis**

# Objectives of Clinical Development Program

- **Demonstrate efficacy similar to standard ESA**
  - Hemoglobin (non-inferiority, primary endpoint)
  - Transfusions
- **Demonstrate safety profile similar to standard ESA**
- **Determine dosing which would achieve stable Hb in desired range**

# Peginesatide Clinical Pharmacology

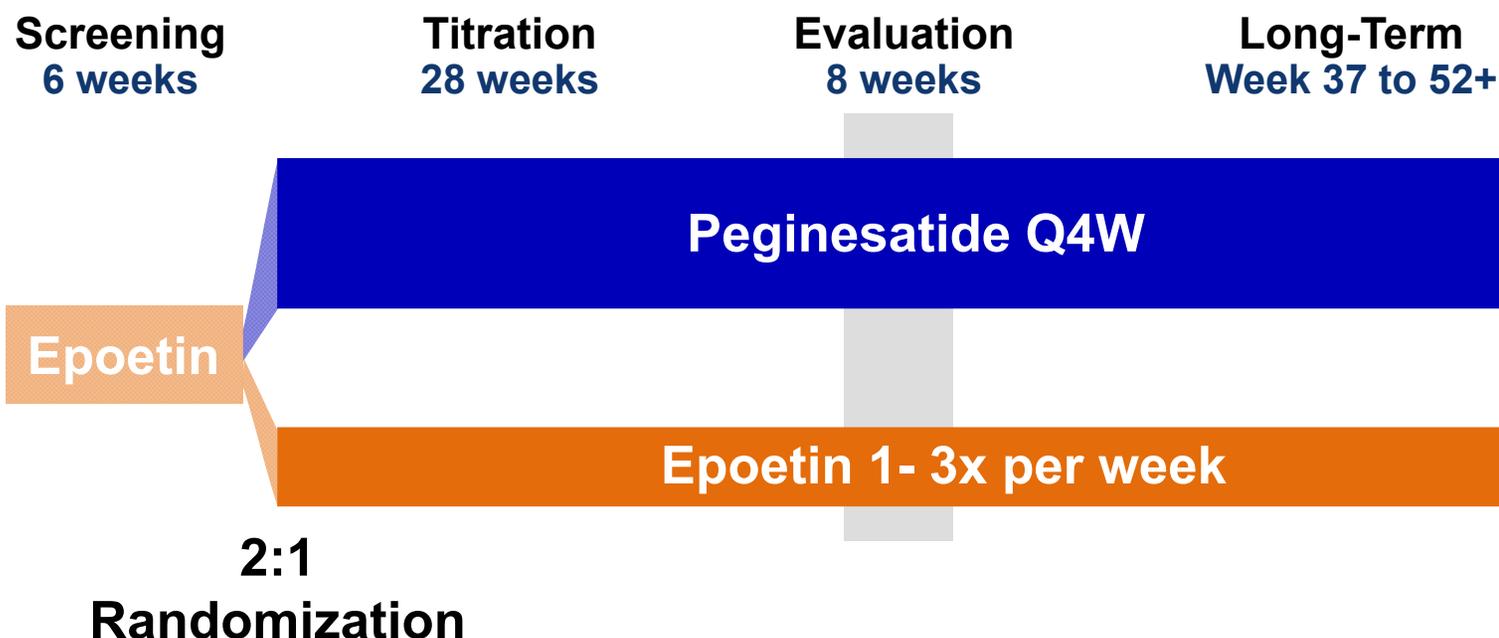
- **$T_{1/2}$  (mean  $\pm$  SD): 48  $\pm$  17 h**
- **Pharmacodynamic response lags systemic exposure**
- **No systemic accumulation with monthly dosing**
- **No drug-drug interactions anticipated**
  - Does not bind to serum albumin
  - Does not induce or inhibit CYP enzymes
- **PK/PD not altered by age, gender, race, common concomitant medications**

# Clinical Development Program

		Number Receiving Peginesatide	Composite CV Safety Endpoint
<b>Phase 1</b>	<b>First-in-human, BA/BE, QTc</b>	<b>300</b>	
<b>Phase 2</b>	<b>PK, efficacy, safety, dosing, PRCA</b>	<b>780</b>	
	<b>Study 15: Epoetin-controlled, dialysis pts initiating ESA</b>	<b>76</b>	
<b>Phase 3</b>	<b>Study 11</b>	<b>326</b>	<b>✓</b>
<b>Non-Dialysis</b>	<b>Study 13</b>	<b>330</b>	<b>✓</b>
	<b>Darbepoetin-controlled, Efficacy and Safety in Non-Dialysis</b>		
<b>Phase 3</b>	<b>Study 12</b>	<b>524</b>	<b>✓</b>
<b>Dialysis</b>	<b>Study 14</b>	<b>542</b>	<b>✓</b>
	<b>Epoetin-controlled, Efficacy and Safety in Dialysis</b>		
<b>Total:</b>		<b>2878</b>	

# Study Design

## Phase 3 Dialysis Studies 12 and 14



	Sample Size			Region	Route of Administration
	Peginesatide	Epoetin	Total		
Study 12	524	269	793	US	IV
Study 14	542	273	815	US and EU	IV and SC

# Disposition

## Phase 3 Dialysis Program

	Study 12		Study 14	
	Peginesatide	Epoetin	Peginesatide	Epoetin
	n (%)	n (%)	n (%)	n (%)
<b>Randomized and dosed</b>	<b>524 (100)</b>	<b>269 (100)</b>	<b>542 (100)</b>	<b>273 (100)</b>
<b>Included in primary efficacy analysis</b>	<b>445 (85)</b>	<b>248 (92)</b>	<b>488 (90)</b>	<b>237 (87)</b>
<b>≥1 year study drug exposure</b>	<b>384 (73)</b>	<b>217 (81)</b>	<b>442 (82)</b>	<b>212 (78)</b>

# Baseline Demographics

## Phase 3 Dialysis Program

	Study 12		Study 14	
	Peginesatide N=524	Epoetin N=269	Peginesatide N=542	Epoetin N=273
Age (years) median (range)	58 (20-91)	57 (22-90)	59 (22-93)	59 (22-97)
Gender – male, %	56	54	61	56
Race				
White, %	50	43	65	67
Black, %	45	51	30	28
Ethnicity – hispanic, %	26	26	18	19
BMI (kg/m <sup>2</sup> ) median	29	29	26	26

# Baseline Characteristics and CV Status Phase 3 Dialysis Program

	Study 12		Study 14	
	Peginesatide N=524	Epoetin N=269	Peginesatide N=542	Epoetin N=273
	%	%	%	%
<b>On Dialysis &gt;1 year</b>	<b>91</b>	<b>88</b>	<b>85</b>	<b>85</b>
<b>Hypertension</b>	<b>99</b>	<b>99</b>	<b>96</b>	<b>97</b>
<b>Diabetes</b>	<b>57</b>	<b>56</b>	<b>44</b>	<b>45</b>
<b>Congestive heart failure</b>	<b>45</b>	<b>47</b>	<b>38</b>	<b>34</b>
<b>Coronary artery disease</b>	<b>45</b>	<b>37</b>	<b>39</b>	<b>33</b>
<b>hsCRP &gt;10 mg/L</b>	<b>31</b>	<b>34</b>	<b>30</b>	<b>29</b>

# Primary Efficacy Endpoint Phase 3 Dialysis Program

## Primary Endpoint

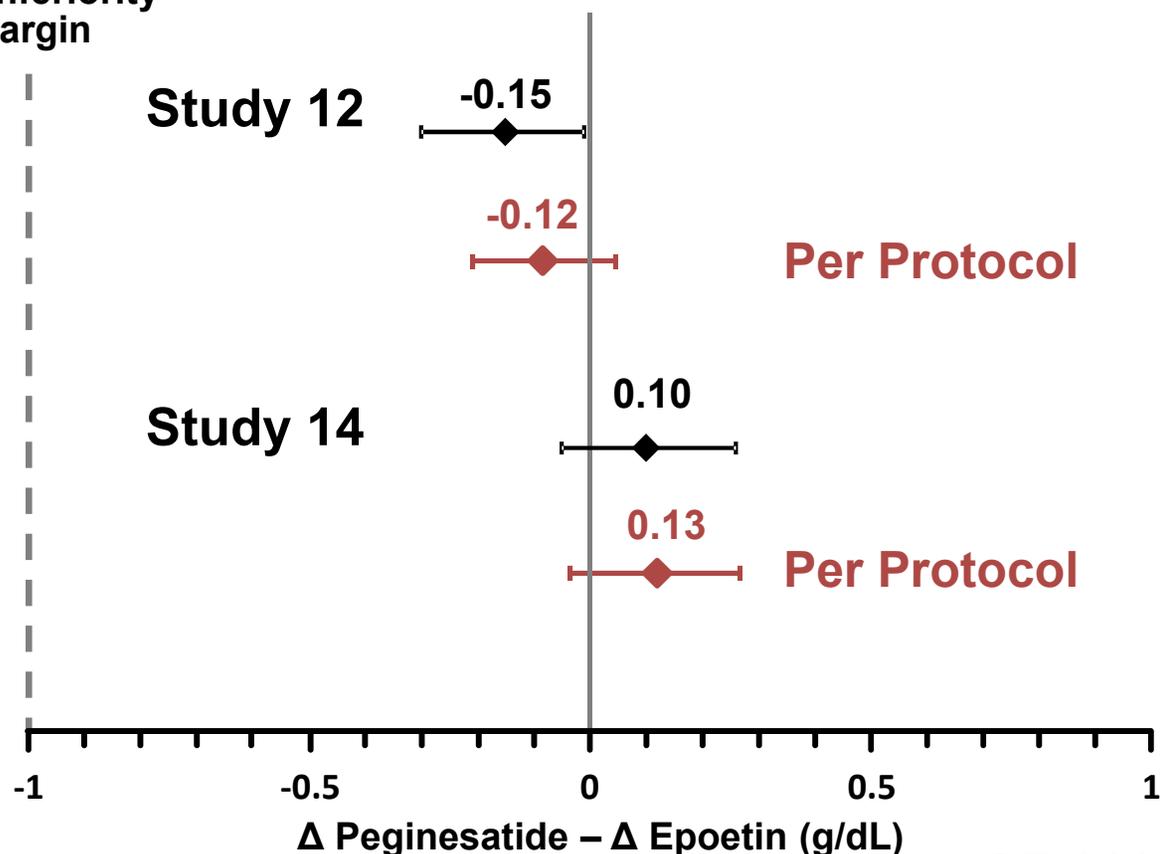
=  $\Delta$  = Mean Change in Hb from Baseline to Evaluation Period

Study 12	
$\Delta$ Peginesatide	$\Delta$ Epoetin
-0.24 g/dL	-0.09 g/dL
Study 14	
$\Delta$ Peginesatide	$\Delta$ Epoetin
-0.07 g/dL	-0.17 g/dL

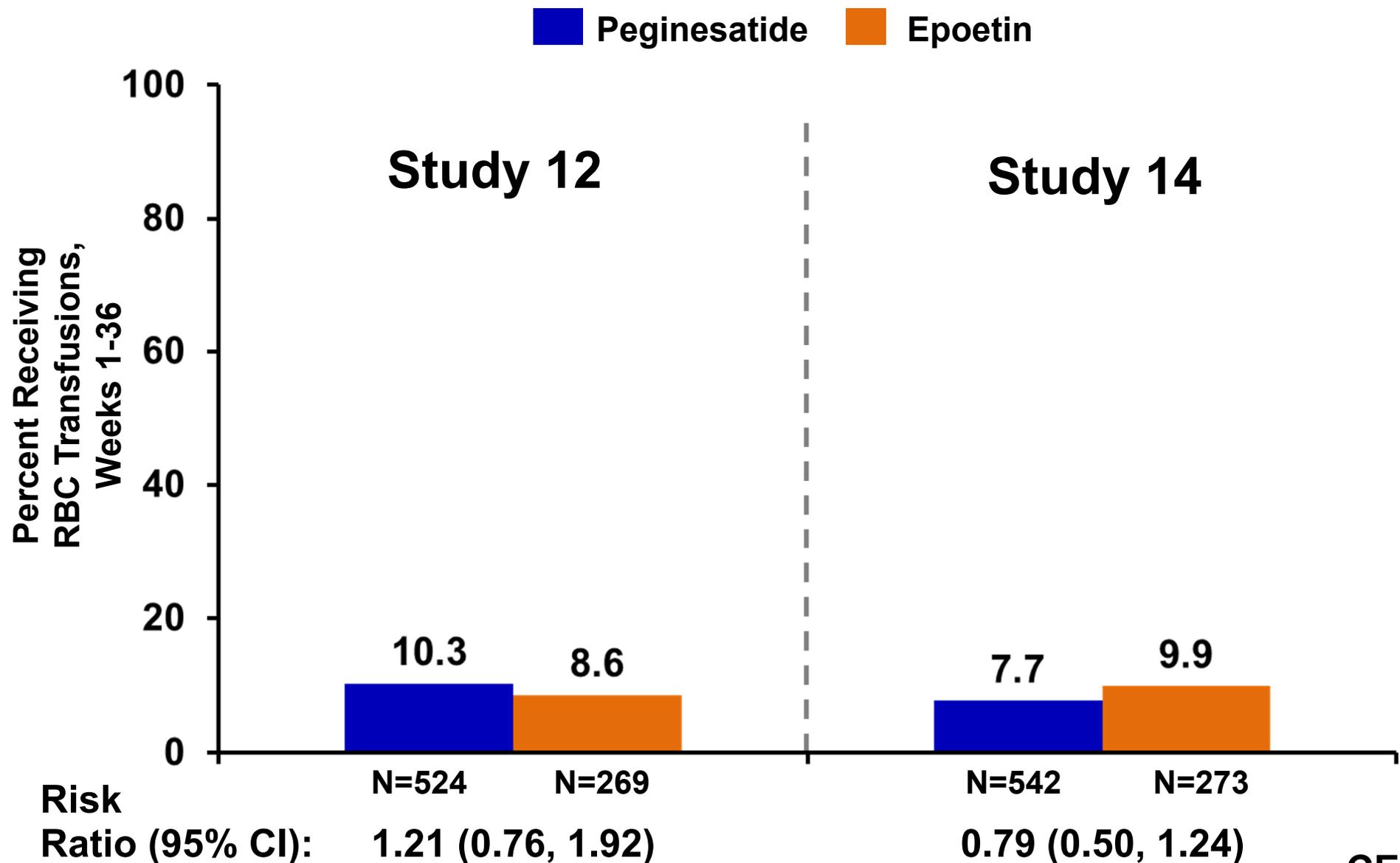
## Non-inferiority Criterion Met

Between-Group Difference  
( $\Delta$  Peginesatide –  $\Delta$  Epoetin)  
with 95% CI (g/dL)

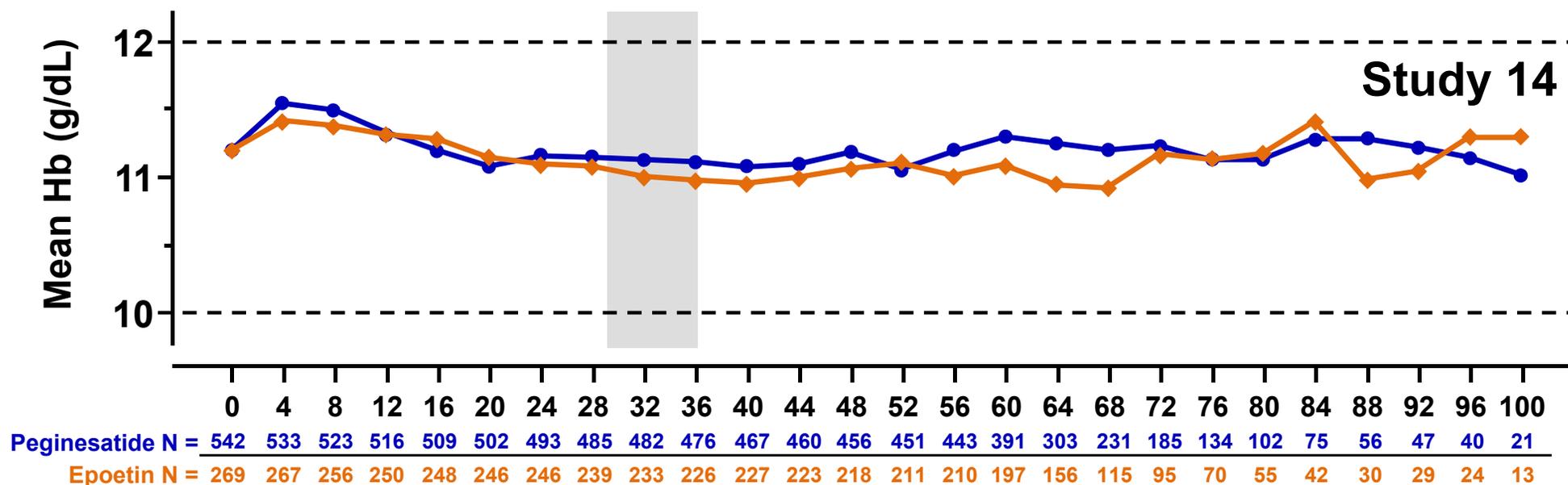
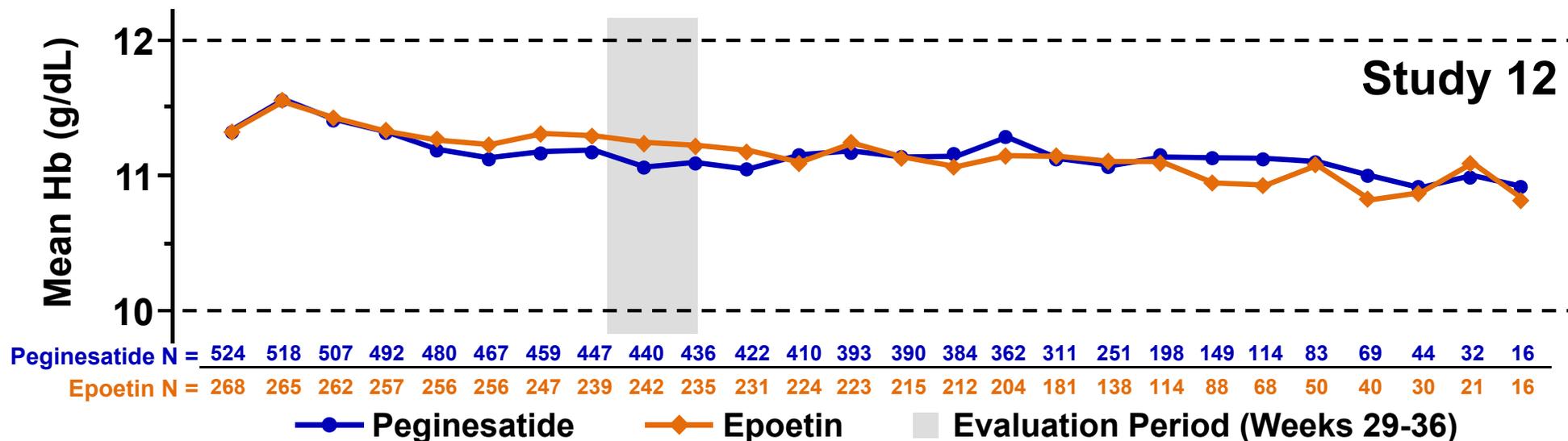
Non-inferiority  
margin



# Secondary Efficacy Endpoint: Patients Receiving RBC Transfusions During Weeks 1-36 Phase 3 Dialysis Program



# Mean Hb Profiles Over Time Phase 3 Dialysis Program

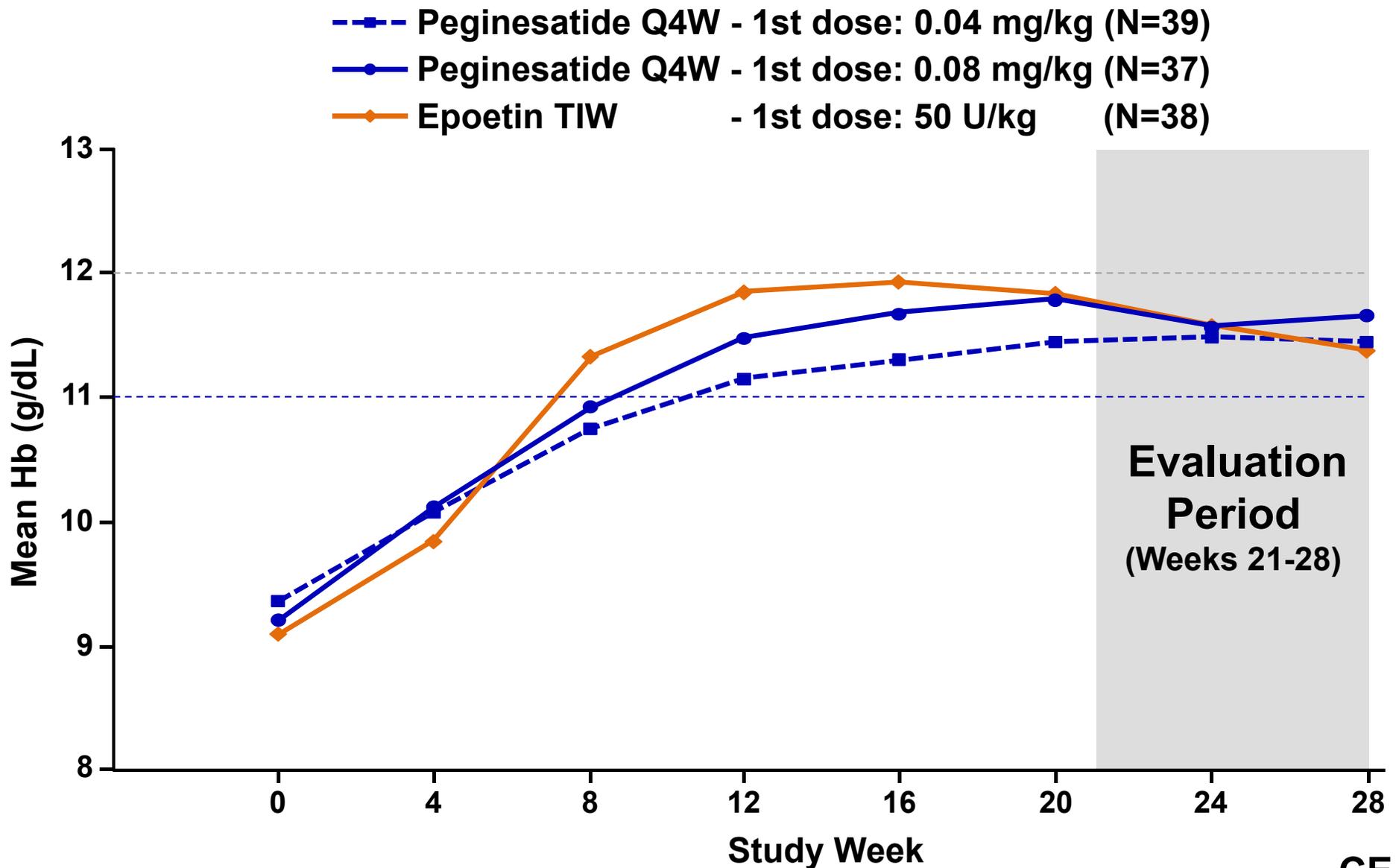


# Dialysis Study 15

- **Objective: Assess safety and efficacy of peginesatide in dialysis patients not previously receiving an ESA**
- **114 dialysis patients not receiving ESAs randomized to:**
  1. Peginesatide – first dose 0.04 mg/kg
  2. Peginesatide – first dose 0.08 mg/kg
  3. Epoetin – labeled starting dose
- **After first dose, individualized dose adjustments as needed to increase and maintain Hb**

# Mean Hb Profiles Over Time

## Dialysis Study 15



# Peginesatide Dosing Recommendations in Dialysis

- **First dose in patients converting from epoetin:**

<b>Previous Epoetin Dose (U/week)</b>	<b>Peginesatide Dose (mg/month)</b>
<b>&lt;2,500</b>	<b>2</b>
<b>2,500 to &lt;4,300</b>	<b>3</b>
<b>4,300 to &lt;6,500</b>	<b>4</b>
<b>6,500 to &lt;8,900</b>	<b>5</b>
<b>8,900 to &lt;13,000</b>	<b>6</b>
<b>13,000 to &lt;19,000</b>	<b>8</b>
<b>19,000 to &lt;33,000</b>	<b>10</b>
<b>33,000 to &lt;68,000</b>	<b>15</b>
<b>≥68,000</b>	<b>20</b>

# **Peginesatide Dosing Recommendations in Dialysis (continued)**

- **First dose in patients not currently receiving an ESA: 0.04 to 0.08 mg/kg**
- **After first dose: Dose adjustments as needed**
- **Peginesatide dosing recommendations are consistent with current ESA labeling**

# Efficacy Summary in Dialysis

- **Peginesatide efficacy similar to epoetin**
  - Primary efficacy endpoint met in each Phase 3 study
  - Transfusion rates low and similar
- **Efficacy demonstrated across broad patient range, representative of US dialysis population**
- **Once monthly peginesatide achieved stable Hb, similar to epoetin dosed up to 3x per week**

# Safety Presentation

- **Patient exposure**
- **AEs, SAEs, ESA class effects in dialysis**
- **Immunogenicity**
- **Composite Safety Endpoint (CSE)**

# Dialysis and Non-Dialysis Phase 3 Programs

<b>Program</b>	<b>Studies</b>	<b>Peginesatide</b>	<b>Comparator</b>	<b>Totals</b>
<b>Dialysis</b>	<b>Studies 12, 14</b>	<b>1066</b>	<b>Epoetin: 542</b>	<b>1608</b>
<b>Non-Dialysis</b>	<b>Studies 11, 13</b>	<b>656</b>	<b>Darbepoetin: 327</b>	<b>983</b>
<b>Overall Phase 3</b>		<b>1722</b>	<b>869</b>	<b>2591</b>

# On Study Duration

## Phase 3 Dialysis and Non-Dialysis

Patient Follow-up Years	Dialysis		Non-Dialysis	
	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)
Average per patient	1.24	1.25	1.37	1.41
Total	1317	677	897	460

# Overview of AEs and SAEs Phase 3 Dialysis Program

	Dialysis	
	Peginesatide N=1066 %	Epoetin N=542 %
<b>AEs</b>	<b>95</b>	<b>93</b>
<b>AEs <math>\geq</math> Grade 3</b>	<b>52</b>	<b>53</b>
<b>SAEs</b>	<b>54</b>	<b>57</b>
<b>AEs leading to treatment D/C</b>	<b>13</b>	<b>12</b>

# ESA Class Events

## Phase 3 Dialysis Program

	Dialysis	
	Peginesatide N=1066 %	Epoetin N=542 %
Hypertension	19.5	18.6
Venous thromboembolic event	2.0	1.7
Arteriovenous access thrombosis	18.1	19.7
Convulsion	2.2	2.0
Malignancy	3.9	4.2

# Immunogenicity

## Overall Safety Population

- **1.2% of patients had Abs to peginesatide**
  - Approximately half of Ab+ patients showed reduced efficacy
    - No Ab+ patients developed Ab to EPO or epoetin
  - Ab+ not associated with hypersensitivity reactions
- **No evidence of immunological cross-reactivity with EPO**
  - No pure red cell aplasia (PRCA)
  - Ongoing study in PRCA (n=18), anemia corrected and chronic transfusions eliminated

# Composite Safety Endpoint (CSE)

## Six CSE Component Events

1. Death (all causes)
2. Stroke
3. Myocardial infarction
4. Congestive heart failure (SAE)
5. Unstable angina (SAE)
6. Arrhythmia (SAE)

- First Phase 3 program with head-to-head comparison of CV safety outcomes
- CSE assessed in the four Phase 3 studies
- Independent, blinded adjudication of potential CSE events

# Sensitivity Analyses Included MACE

## Six CSE Component Events

1. Death (all causes)
2. Stroke
3. Myocardial infarction
4. Unstable angina (SAE)
5. Congestive heart failure (SAE)
6. Arrhythmia (SAE)

**MACE**  
**(Major Adverse  
Cardiovascular Event)**  
**= Death, Stroke, MI**

# CSE Plan and Methods

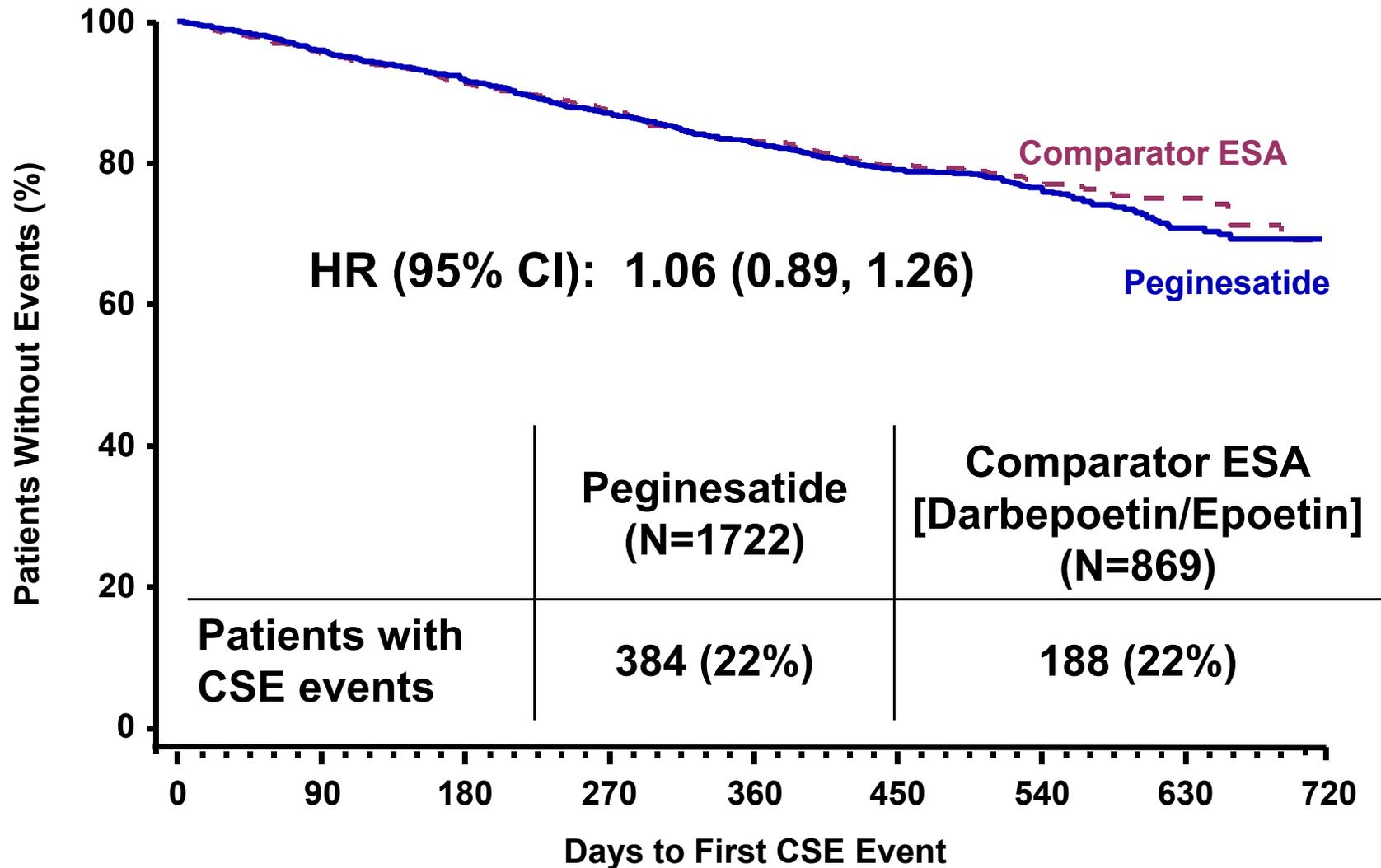
- **Pre-specified analysis plan:**
  - Primary analysis: Dialysis and non-dialysis combined
  - Also pre-specified: Dialysis, non-dialysis separately
- **Sample size and follow-up sufficient to exclude hazard ratios  $>1.3$  in primary analysis**
  - Based on previous CV outcome studies of ESAs
  - Consistent with FDA 2008 guidance for diabetic therapies

# Presentation of CSE

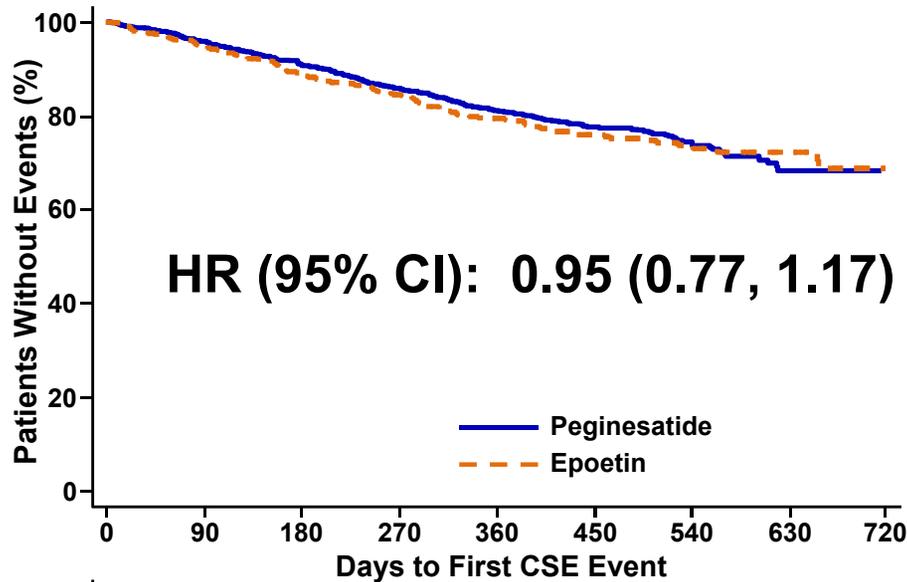
- ➔ **CSE findings combined and by population**
- **Detailed examination of CSE in Non-Dialysis**
- **Detailed examination of CSE in Dialysis**

# Primary CSE Analysis

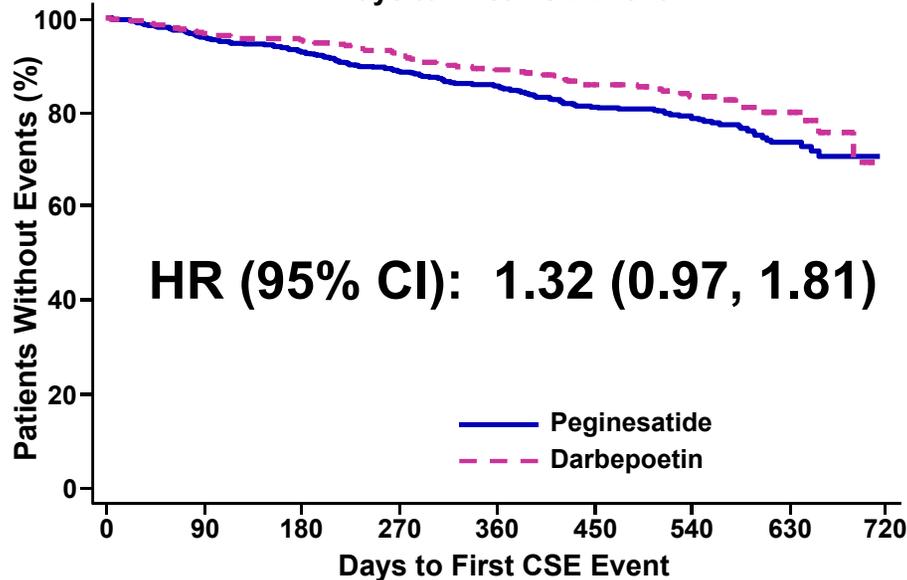
## Dialysis and Non-Dialysis Combined



# Pre-specified CSE Analysis by Population



	Dialysis	
	Peginesatide (N=1066)	Epoetin (N=542)
<b>Patients with CSE events</b>	<b>243 (23%)</b>	<b>132 (24%)</b>



	Non-Dialysis	
	Peginesatide (N=656)	Darbepoetin (N=327)
<b>Patients with CSE events</b>	<b>141 (22%)</b>	<b>56 (17%)</b>

# CSE Component Events in Dialysis

	Dialysis	
	Peginesatide N=1066	Epoetin N=542
	n (%)	n (%)
<b>Patients with CSE Events</b>	<b>243 (22.8)</b>	<b>132 (24.4)</b>
<b>Patients with CSE Component Events:</b>		
<b>Death</b>	<b>115 (10.8)</b>	<b>64 (11.8)</b>
<b>Stroke</b>	<b>26 (2.4)</b>	<b>20 (3.7)</b>
<b>MI</b>	<b>49 (4.6)</b>	<b>29 (5.4)</b>
<b>Unstable angina</b>	<b>24 (2.3)</b>	<b>12 (2.2)</b>
<b>CHF</b>	<b>103 (9.7)</b>	<b>49 (9.0)</b>
<b>Arrhythmia</b>	<b>63 (5.9)</b>	<b>35 (6.5)</b>

Table rows are not mutually exclusive.

# CSE Component Events in Non-Dialysis

	Non-Dialysis	
	Peginesatide N=656	Darbepoetin N=327
	n (%)	n (%)
<b>Patients with CSE Events</b>	<b>141 (21.5)</b>	<b>56 (17.1)</b>
<b>Patients with CSE Component Events:</b>		
<b>Death</b>	<b>58 (8.8)</b>	<b>22 (6.7)</b>
<b>Stroke</b>	<b>7 (1.1)</b>	<b>3 (0.9)</b>
<b>MI</b>	<b>24 (3.7)</b>	<b>11 (3.4)</b>
<b>Unstable angina</b>	<b>16 (2.4)</b>	<b>3 (0.9)</b>
<b>CHF</b>	<b>56 (8.5)</b>	<b>28 (8.6)</b>
<b>Arrhythmia</b>	<b>37 (5.6)</b>	<b>13 (4.0)</b>

Table rows are not mutually exclusive.

# Presentation of CSE

- CSE findings combined and by population
- ➔ **Detailed examination of CSE in Non-Dialysis**
- **Detailed examination of CSE in Dialysis**

# Evaluation of CSE Findings in Non-Dialysis

- **Potential mechanisms did not explain observed differences, including:**
  - Dose/exposure: Higher doses in dialysis
    - Median peginesatide dose during Phase 3 Evaluation Period: **5.1 mg** in dialysis vs **1.9 mg** in non-dialysis
  - Treatment initiation: Events not clustered at initiation or after Hb increases
  - Blood pressure: No treatment differences

# Evaluation of CSE Findings in Non-Dialysis

- **Contributing factors**
  - Smaller sample size
  - Baseline imbalances

# Baseline Distribution of CV Risk in Non-Dialysis

Baseline CV Risk Factor	Non-Dialysis Studies 11 and 13	
	Peginesatide %	Darbepoetin %
Male	44	39
BMI $\geq 30$ kg/m <sup>2</sup>	48	44
Diabetes	68	60
CAD	40	38
PVD	27	20
Arrhythmia	16	13
Hyperlipidemia	78	74
MI	15	10
NYHA HF Class II-IV	18	15
hsCRP > 10	21	18

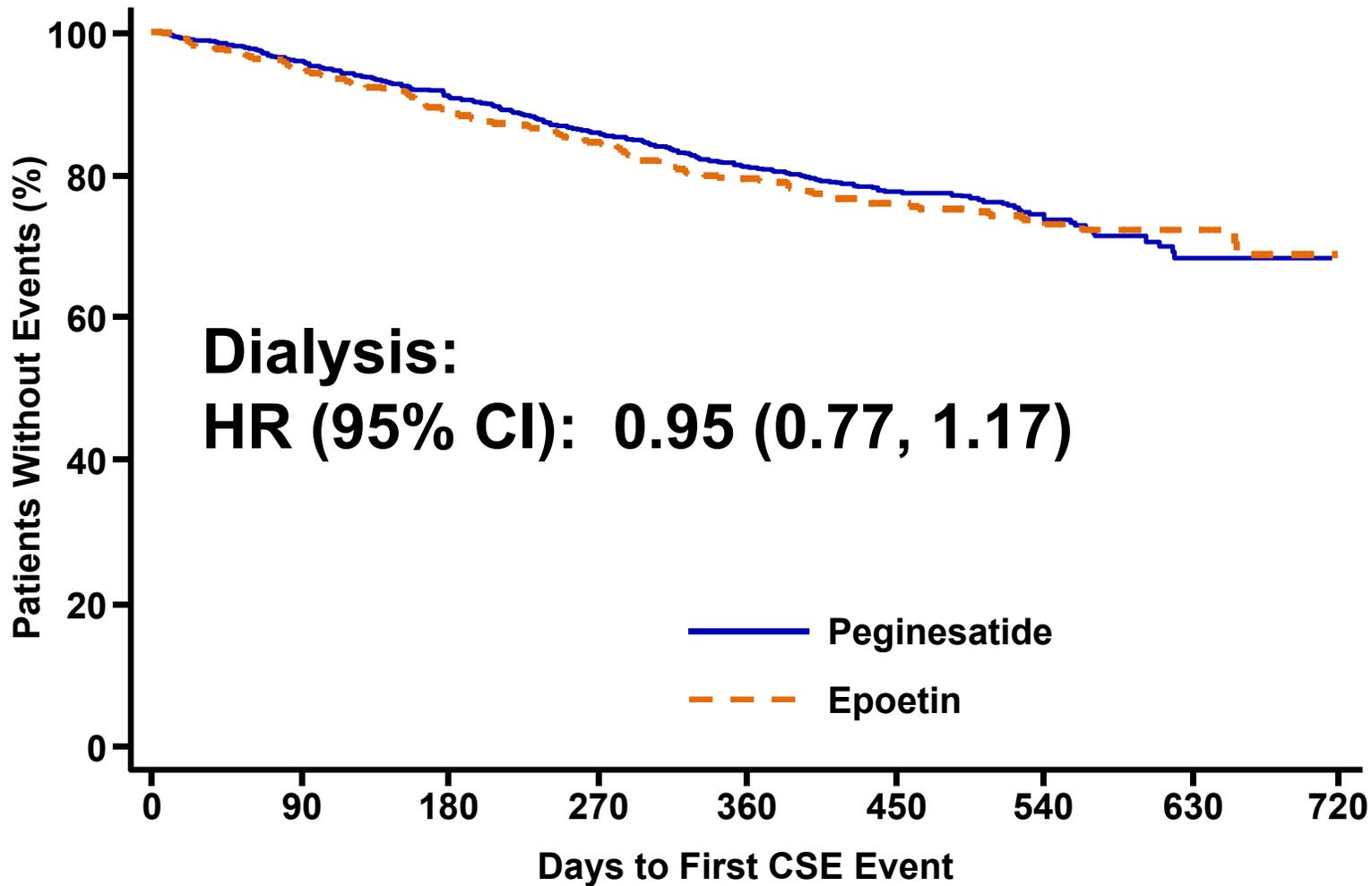
# CSE Findings in Non-Dialysis: Interpretation

- **Cannot definitively exclude a risk in non-dialysis**
- **Investigation of potential mechanisms did not explain observed treatment differences**
- **Potential influence of non-drug factors observed**
  - Baseline imbalances consistently disfavored peginesatide vs darbepoetin

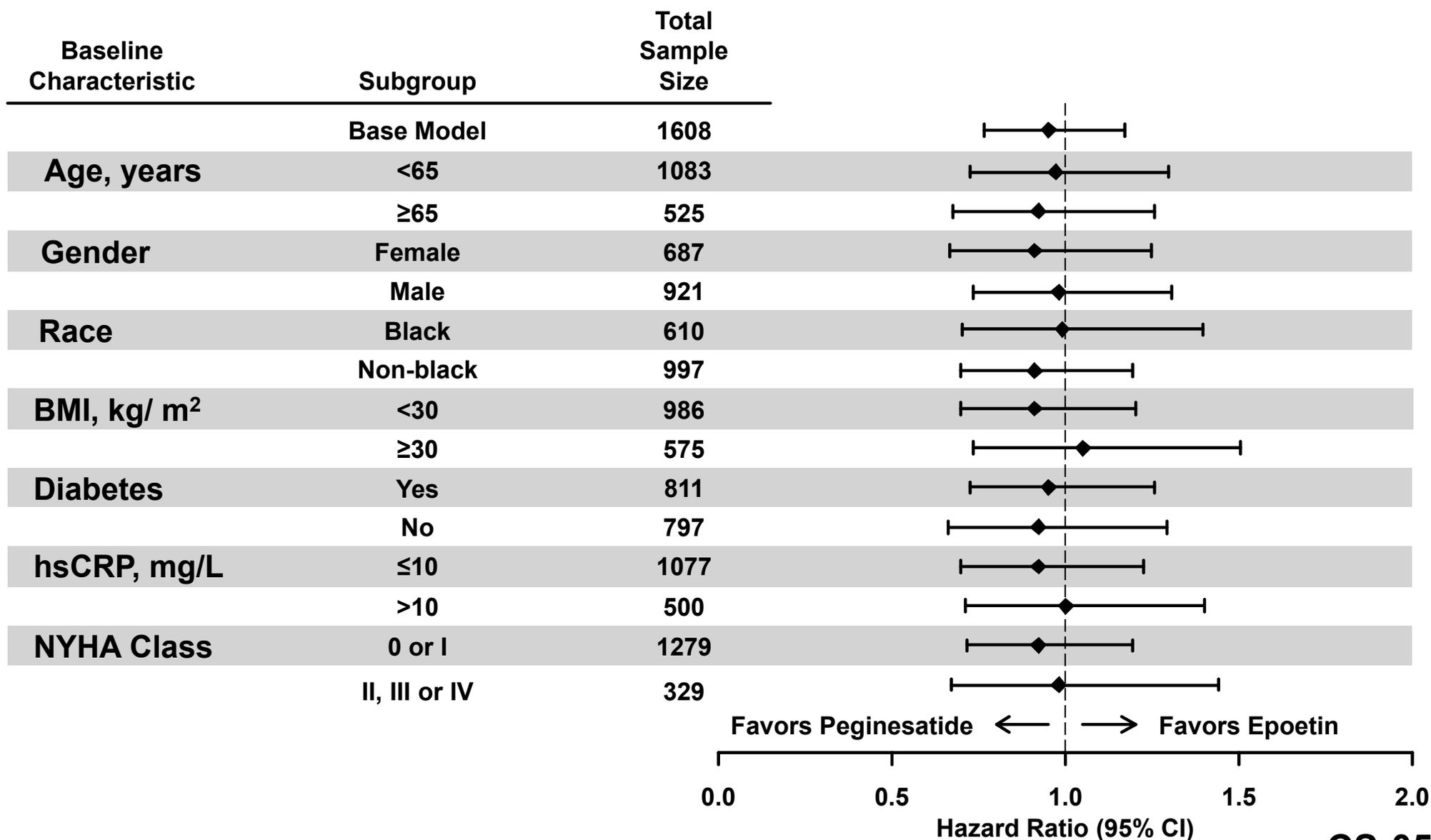
# Presentation of CSE

- CSE findings combined and by population
- Detailed examination of CSE in Non-Dialysis
- ➔ **Detailed examination of CSE in Dialysis**

# CSE Analysis in Dialysis



# Subgroup Analyses of CSE Phase 3 Dialysis Program



# CSE by Individual Study

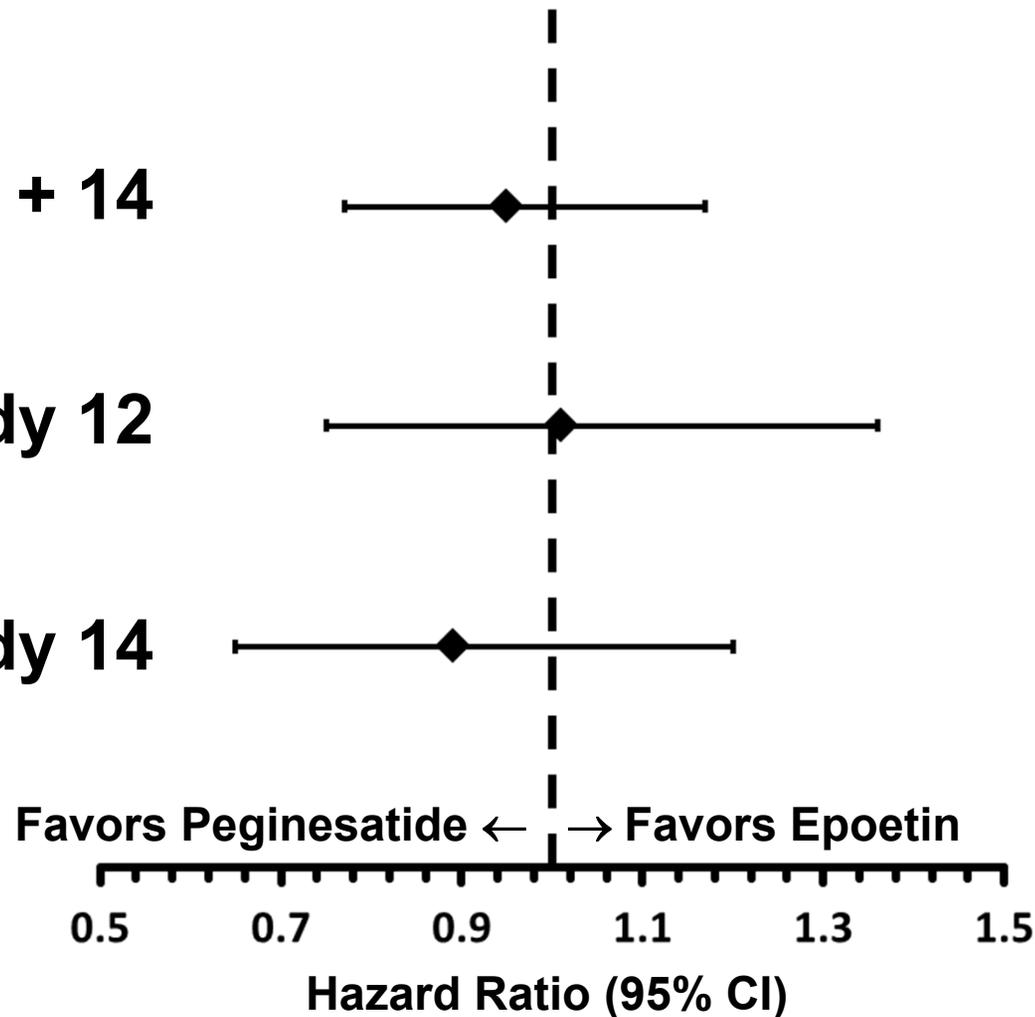
## Phase 3 Dialysis Program

CSE for Dialysis:

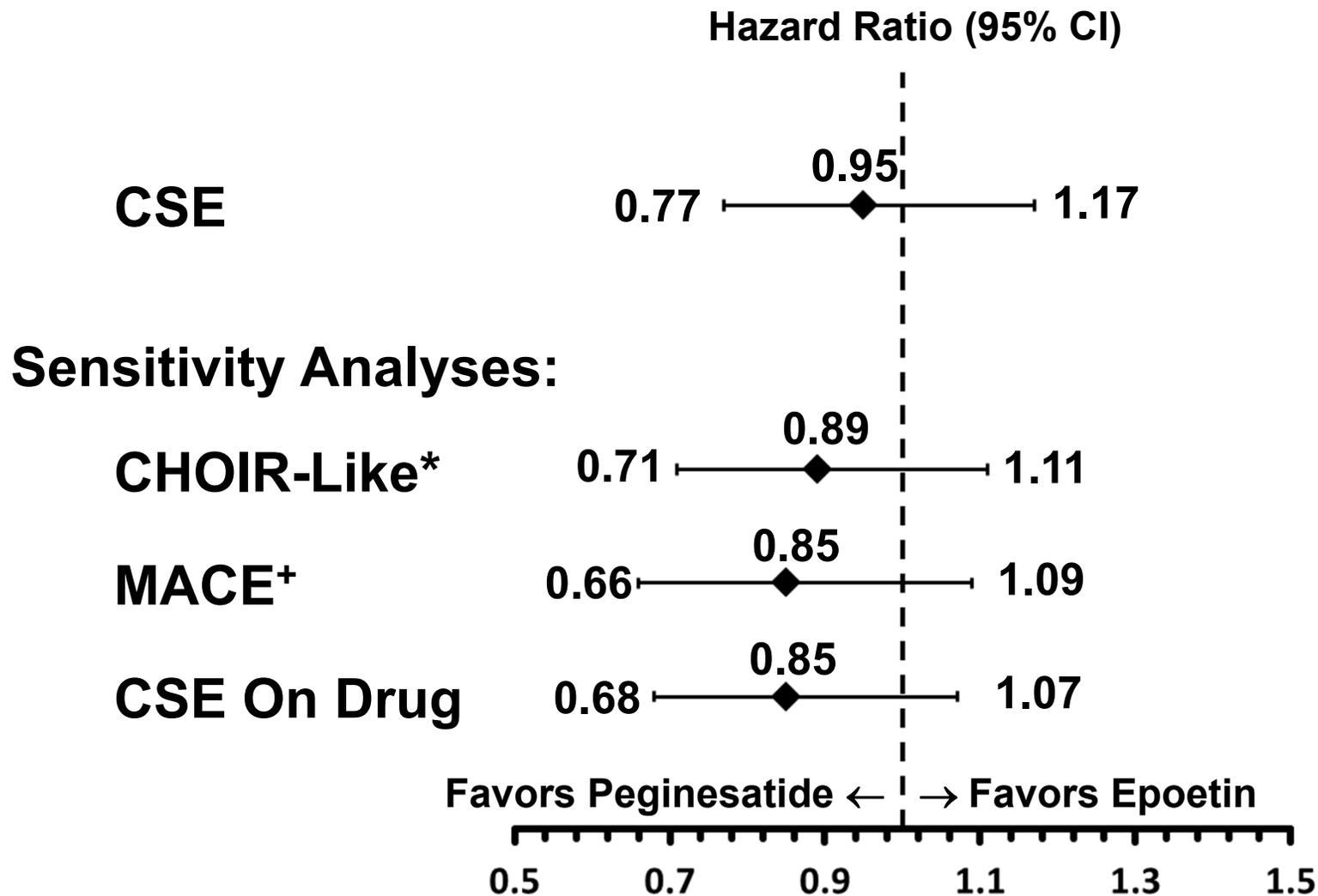
Studies 12 + 14

Study 12

Study 14



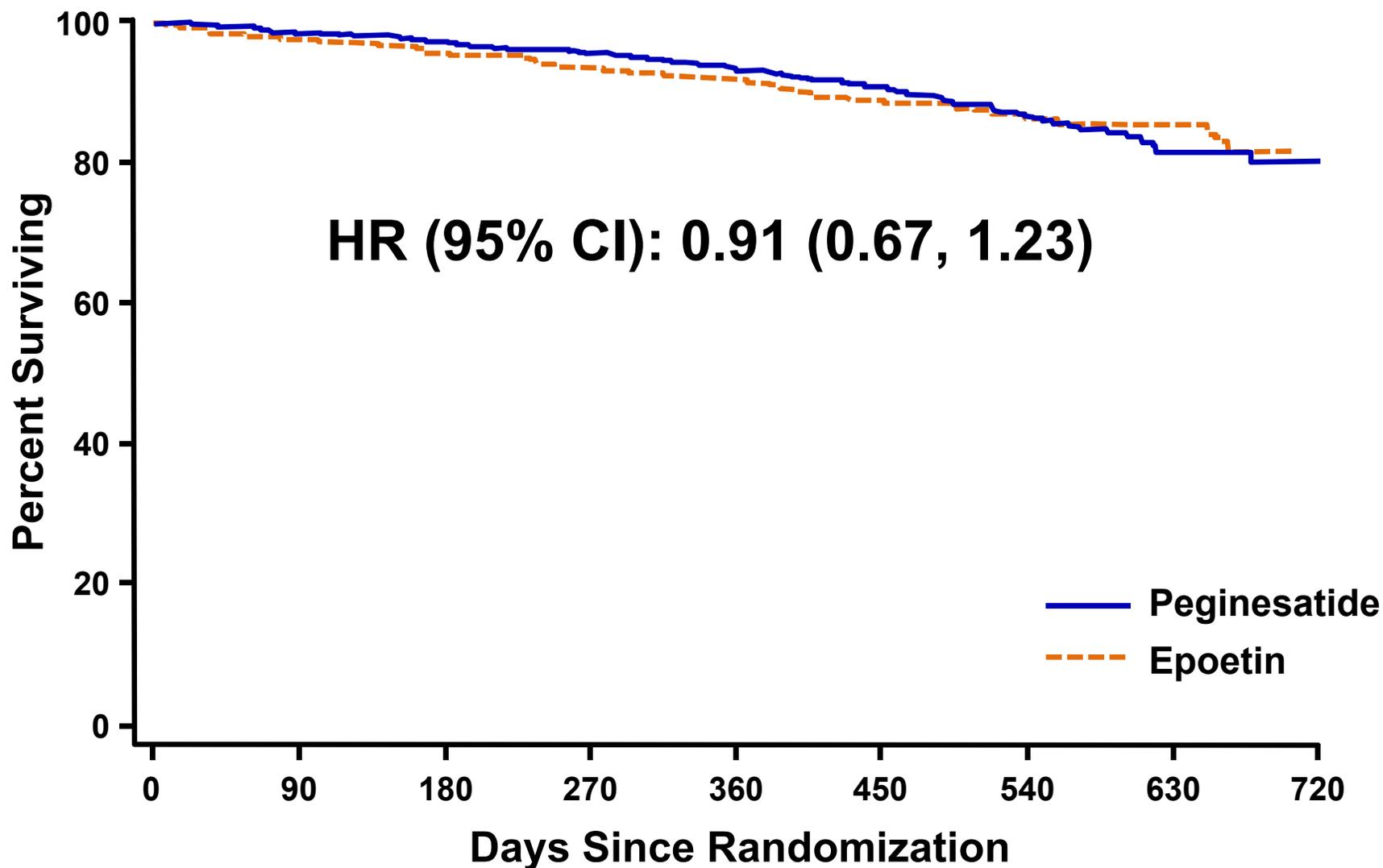
# Summary of CSE and Sensitivity Analyses Phase 3 Dialysis Program



\*CHOIR-Like=Death, Stroke, MI, CHF

+MACE=Death, Stroke, MI

# Survival Analysis (CSE Component: Death) Phase 3 Dialysis Program



# Overall Conclusions – Program in Dialysis

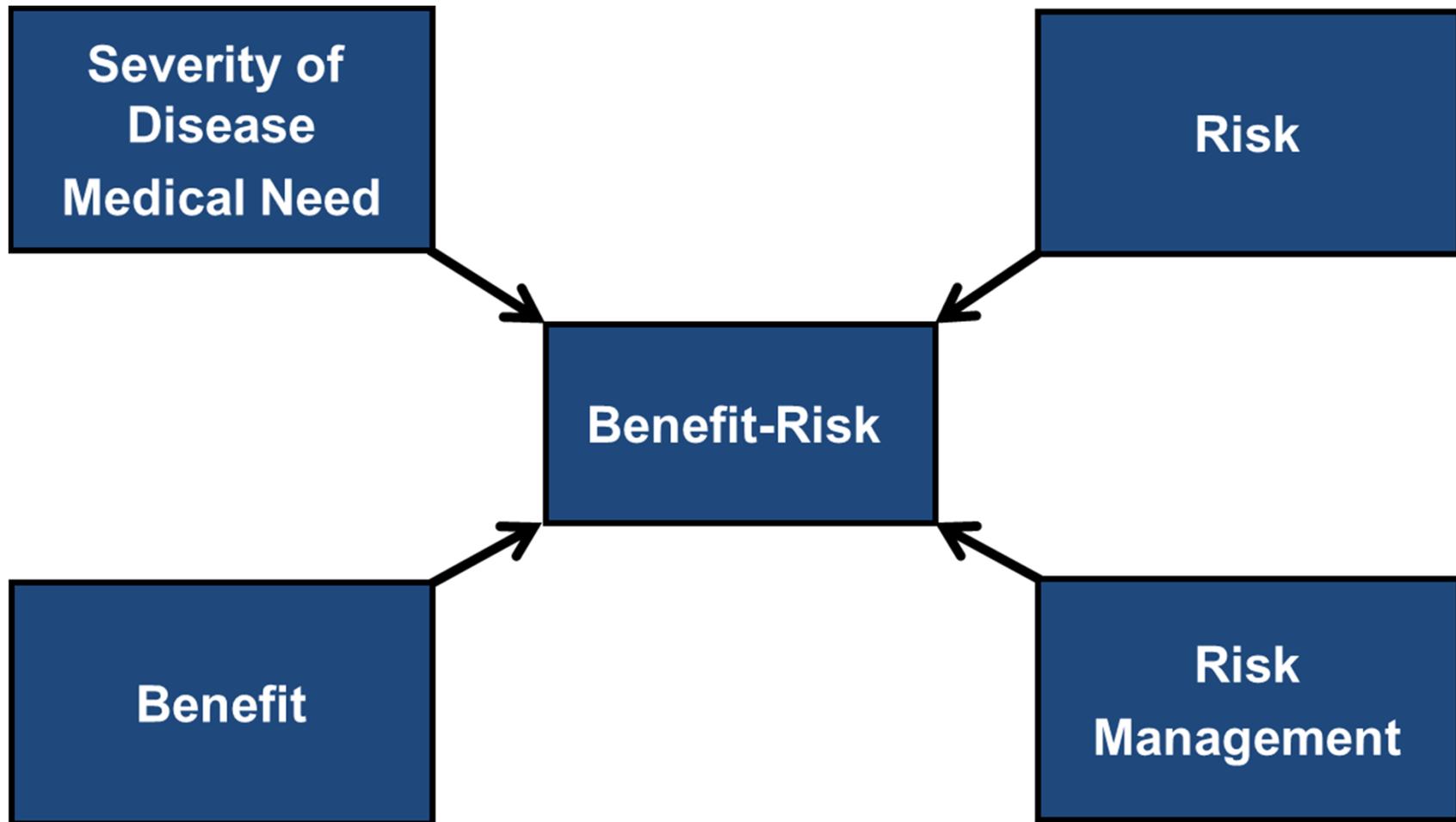
- **Large program in a representative population including two randomized, controlled Phase 3 trials**
- **Efficacy of once monthly peginesatide established**
- **Overall and CV safety profile similar to epoetin**

# Benefit-Risk Summary

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# Assessing Benefit-Risk



# Severity of Disease

	<b>Non-Dialysis</b>	<b>Dialysis</b>
<b>Renal function</b>	<b>CKD stage 3 to 5</b>	<b>Require renal replacement therapy</b>
<b>Severity of anemia</b>	<b>Mild/Moderate</b>	<b>Severe</b>
<b>Need for ESAs:</b> <ul style="list-style-type: none"><li>• <b>Avoid transfusions</b></li><li>• <b>Treat symptoms</b></li></ul>	<b>Varies</b>	<b>Absolute</b>
<b>Cardiovascular risk</b>	<b>High</b>	<b>Higher</b>
<b>Current benefit-risk for ESAs</b>	<b>Less clear</b>	<b>Benefit outweighs risks</b>

# Medical Need for Peginesatide in Dialysis

- **A single agent, epoetin alfa, has been the standard of care in dialysis**
- **Peginesatide developed in collaboration with the nephrology community and their interest in additional ESA therapies**
- **Nephrologists managing complex and diverse set of dialysis patients**
  - Multiple treatment modalities, HD, peritoneal dialysis, home HD
  - Health resource constraints
  - Interest in simplification of anemia management
  - Growing concern about PRCA in light of biosimilars

# Dialysis Program: Benefit and Risks of Peginesatide

## Benefit

- Administered monthly
- Effective in the treatment of anemia
- Similar efficacy relative to the standard of care
- Low transfusion rates

## Risks

- Similar overall and CV safety with comparator
- CSE results consistent by study
- CSE sensitivity analyses with HR <1
- No new identified risks

# Risk Management Plan

- **Risks communicated to HCP and patients:**
  - Prescribing information, DHCP letters, Medication Guide
- **Distribution limited to dialysis centers**
- **Guidance to limit CV risk in dialysis**
  - Monitoring and control BP
  - Keep Hb below 11 g/dL
  - Avoid dose escalations in non-responding patients
- **Post-marketing longitudinal cohort study in dialysis**
  - Focus on CV safety
  - Compare outcomes in peginesatide with standard of care

# Dialysis Benefit Risk Assessment

- **Large dialysis program, 2 pivotal RCTs, conducted to support the indication in dialysis**
- **First head-to-head comparison of CV safety between ESAs**
- **Results consistent with regulatory criteria that peginesatide not be importantly inferior to recombinant ESAs**
- **Benefits outweigh the risks for peginesatide in dialysis**

# Proposed Indication

**Peginesatide is an ESA that is indicated for the treatment of anemia due to chronic kidney disease in adult patients on dialysis.**

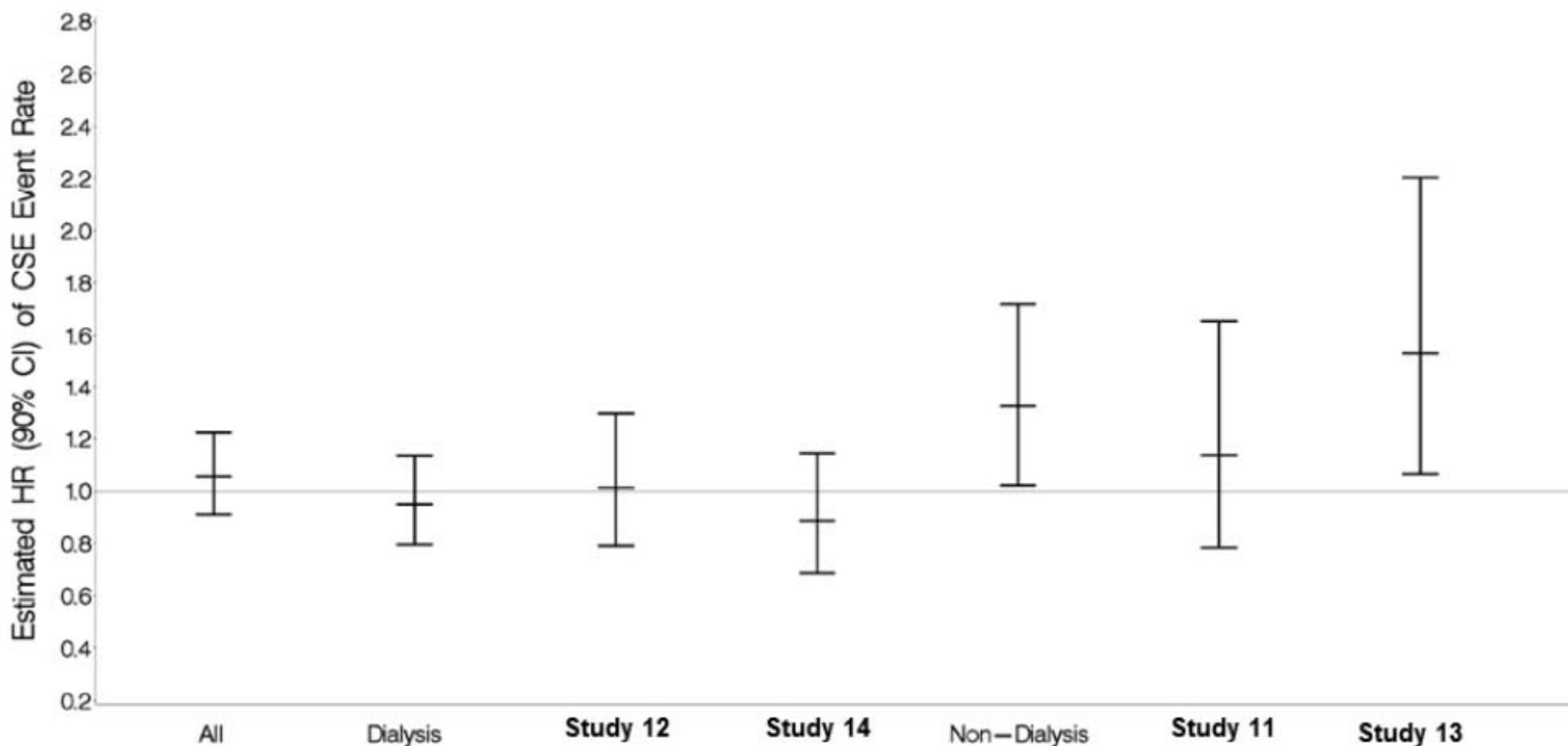
# Vital Status of Patients Prematurely Terminating from Study – Dialysis Population

	Study 12		Study 14		Studies 12 and 14	
	Peginesatide (N=524)	Epoetin (N=269)	Peginesatide (N=542)	Epoetin (N=273)	Peginesatide (N=1066)	Epoetin (N=542)
<b>Patients Prematurely Terminating from Study</b>	<b>134 (25.6%)</b>	<b>56 (20.8%)</b>	<b>90 (16.6%)</b>	<b>52 (19.0%)</b>	<b>224 (21.0%)</b>	<b>108 (19.9%)</b>
<b>Post Termination Vital Status known</b>	<b>117 (22.3%)</b>	<b>49 (18.2%)</b>	<b>72 (13.3%)</b>	<b>46 (16.8%)</b>	<b>189 (17.7%)</b>	<b>95 (17.5%)</b>
<b>Post Termination Vital Status Unknown</b>	<b>17 (3.2%)</b>	<b>7 (2.6%)</b>	<b>18 (3.3%)</b>	<b>6 (2.2%)</b>	<b>35 (3.3%)</b>	<b>13 (2.4%)</b>

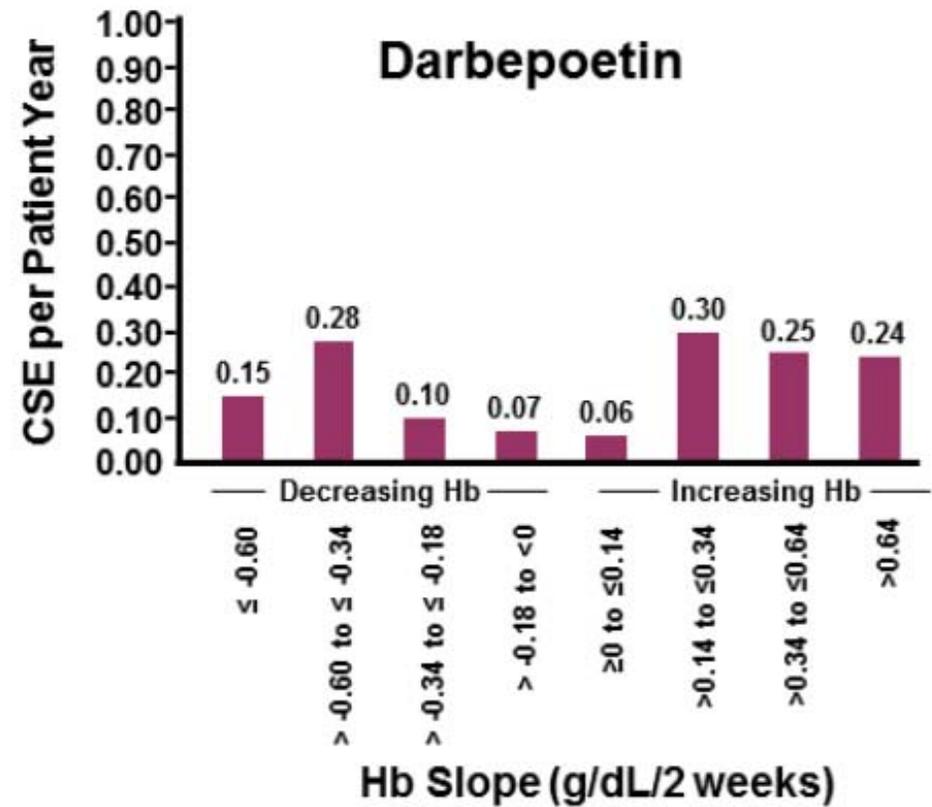
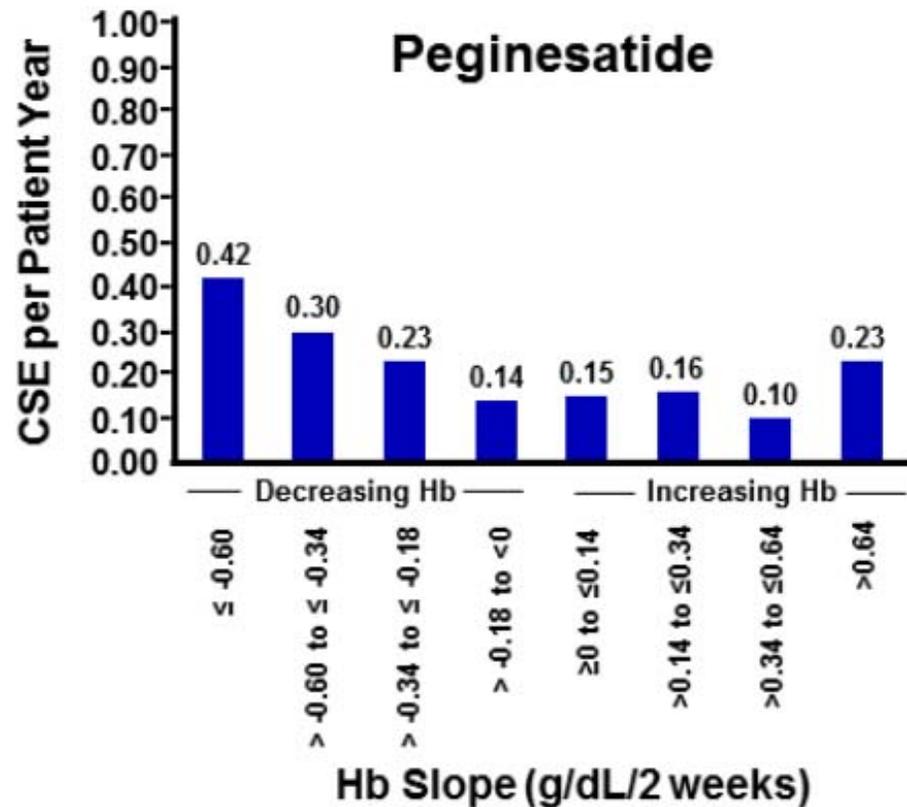
# Duration of Confirmed Hemoglobin Excursions >13.0 g/dL: Studies 12 and 14

Average Duration (Days)	Study 12		Study 14	
	Peginesatide (N=524)	Epoetin (N=269)	Peginesatide (N=542)	Epoetin (N=273)
Through End of Treatment	n=98	n=65	n=138	n=41
Mean (SD)	23.97 (10.833)	22.54 (10.016)	24.62 (11.449)	22.46 (11.149)
Median	22.0	20.0	22.0	20.0
Q1 – Q3	15.0 – 29.0	15.0 – 29.0	16.0 – 29.0	15.0 – 29.0
Min – Max	3.0 – 64.0	4.0 – 60.5	7.0 – 80.0	3.0 – 57.0

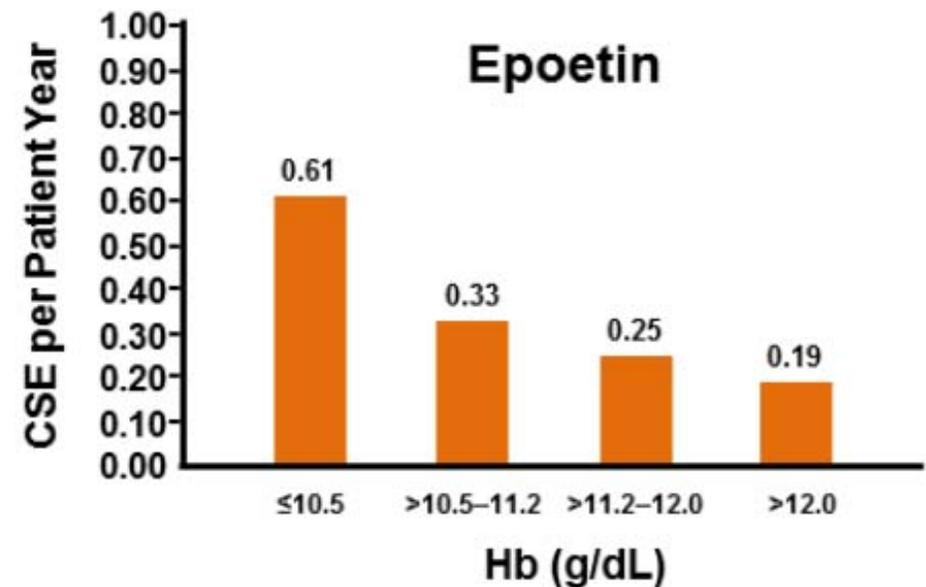
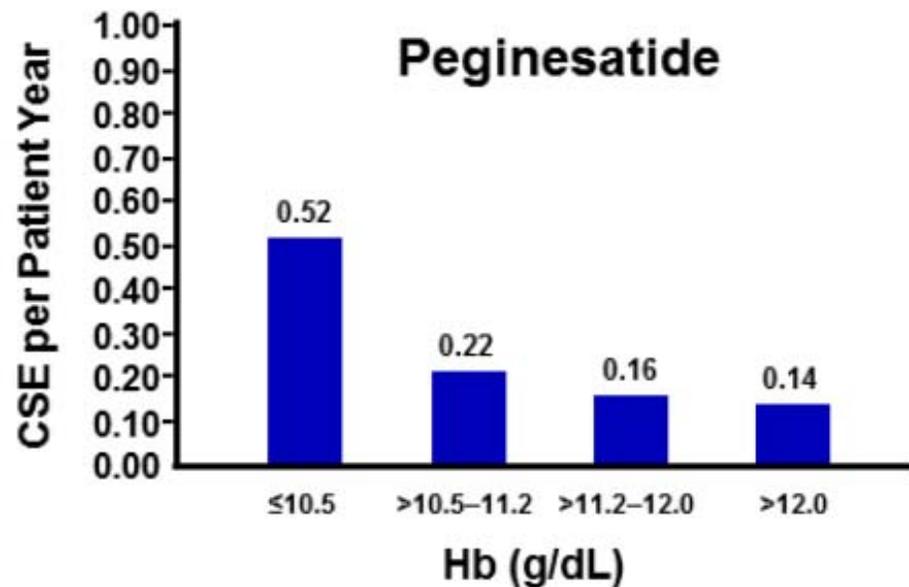
# Estimated Hazard Ratio and 2-Sided 90% CI of CSE by Study and Indication



# CSE by Temporal Hb Slope (Event-Based Analysis) – Non-Dialysis Population



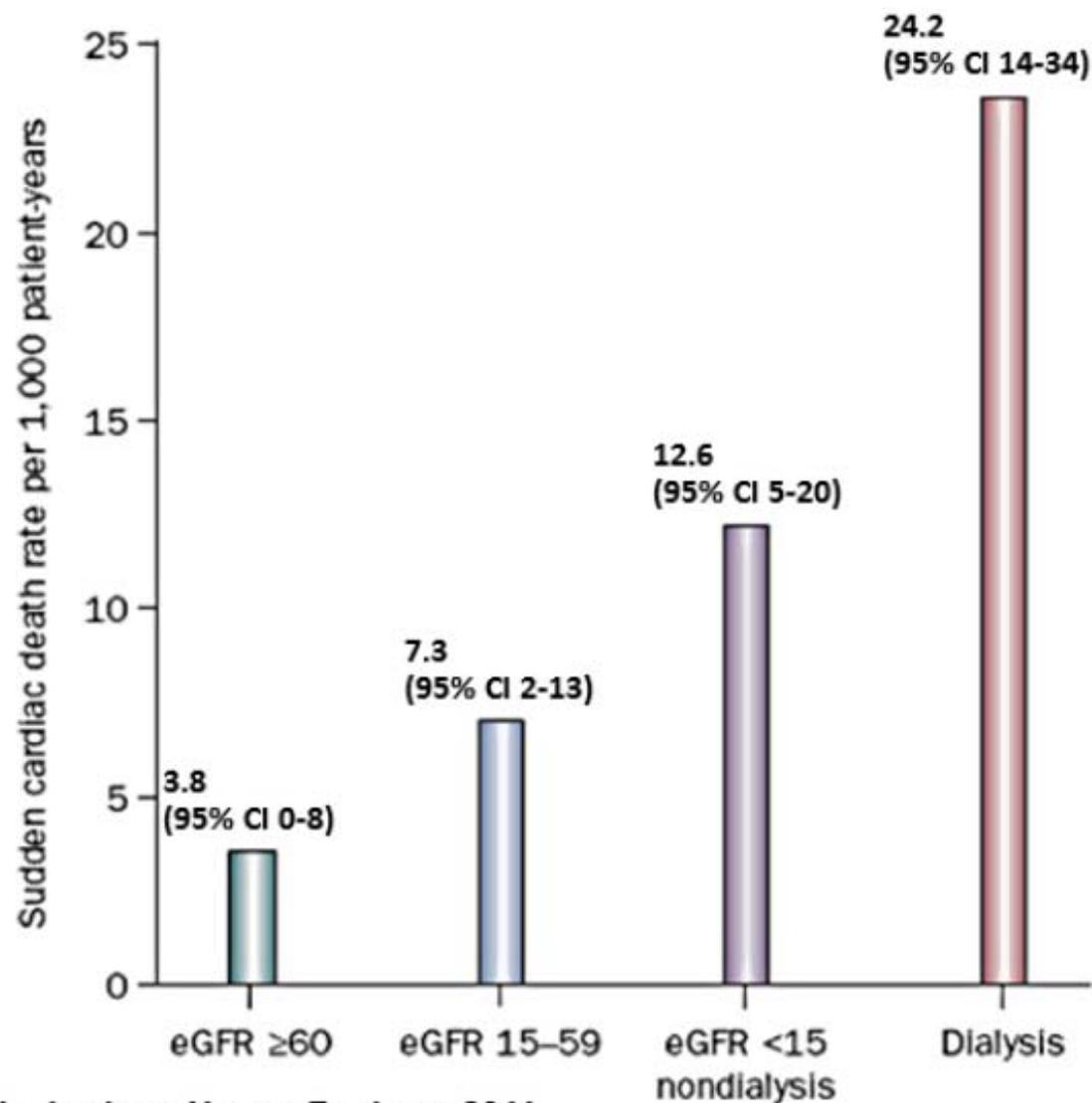
# CSE by Temporal Hb (Event-Based Analysis) – Dialysis Population



# Summary of On-Drug MACE CSE Events – Non-Dialysis Population

Composite Safety Endpoint	Peginesatide (N=656)	Darbepoetin Alfa (N=327)
No. of Patients with Events N (%)	48 (7.3)	22 (6.7)
Hazard Ratio (HR) Relative to Control		
HR	1.14	
95%CI	(0.68, 1.89)	

# Risk of Sudden Death Increases with Worsening CKD



# CSE Adjudicated Cause of Death – Sudden Death in Dialysis Studies 12 and 14, and in Dialysis Population

	Study 12		Study 14		Dialysis Population (Studies 12 & 14)	
	Peginesatide (N=524)	Epoetin (N=269)	Peginesatide (N=542)	Epoetin (N=273)	Peginesatide (N=1,066)	Epoetin (N=542)
<b>N (%) On Study Cause of Death = Sudden Death</b>	13 (2.5%)	6 (2.2%)	13 (2.4%)	6 (2.2%)	26 (2.4%)	12 (2.2%)

# Event Review Committee Process Flow

