

Epoetin Hospira Biosimilar Application to Epogen[®]/Procrit[®] (epoetin alfa)

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FDA Oncologic Drugs Advisory Committee
Hospira Inc., a Pfizer company

Introduction

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Pfizer Essential Health

Epoetin Hospira as a Biosimilar to Reference Product Epogen/Procrit

- Single Biologics License Application (BLA) approved in 1989
- Not seeking interchangeability designation

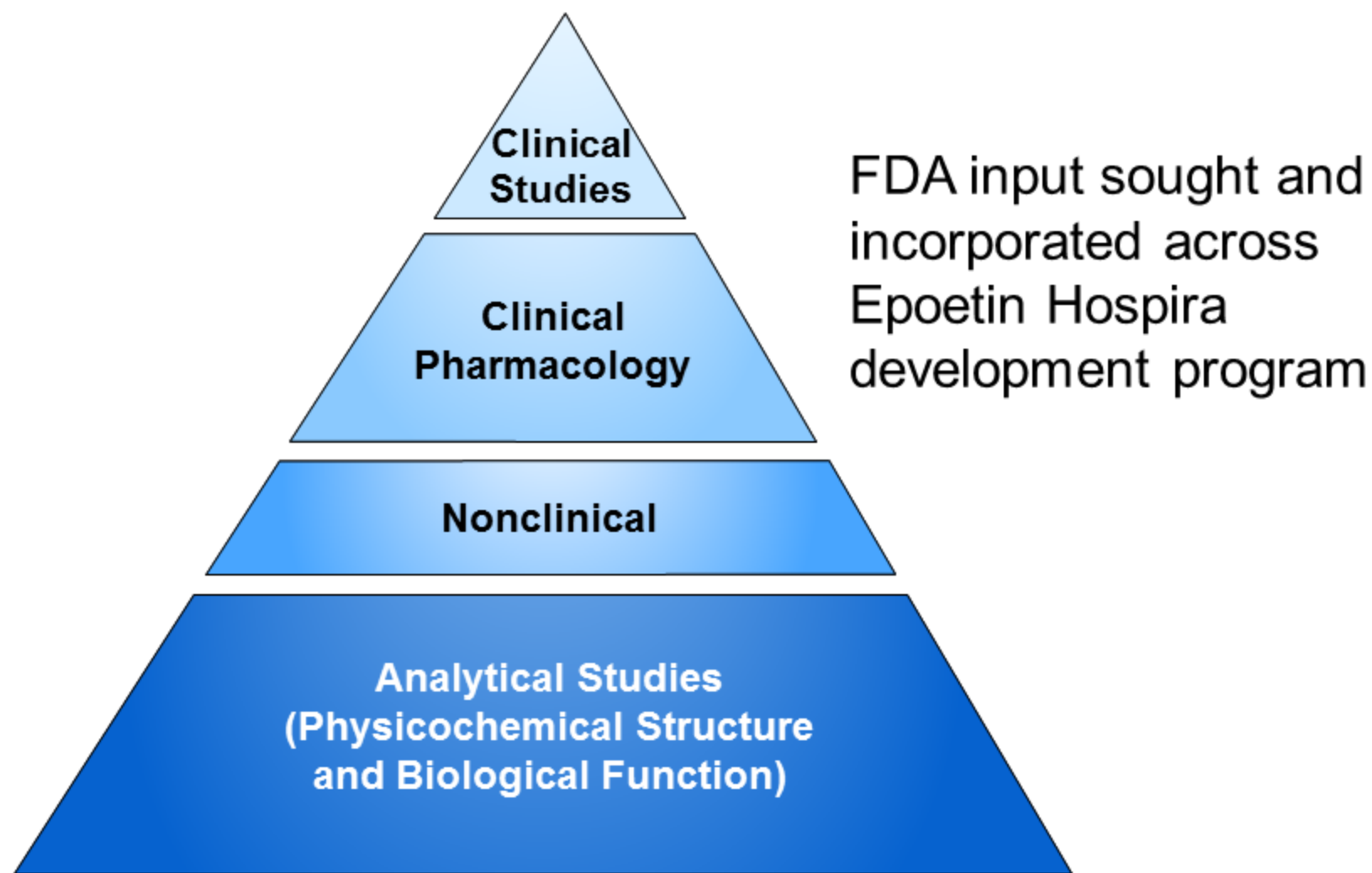
Seeking Approval for All Epogen and Procrit Indications

- Treatment of anemia
 - Chronic kidney disease (CKD), with and without dialysis
 - Zidovudine treatment in HIV patients
 - Myelosuppressive chemotherapy in non-myeloid malignancies
- Reduce allogeneic red blood cell (RBC) transfusions
 - Elective, noncardiac, nonvascular surgery

Epoetin Hospira Development Based on Retacrit Approved in Europe

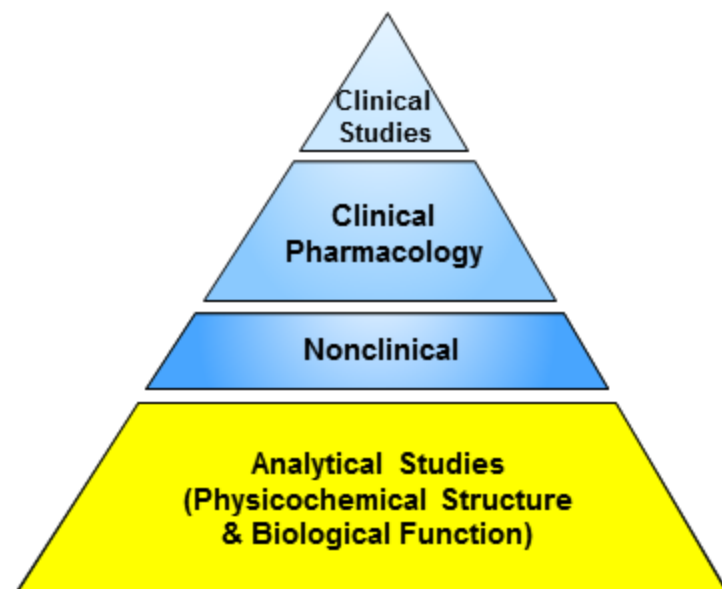
- Retacrit
 - Approved in Europe in 2007 as biosimilar to Eprex[®] reference product
 - >363,000 patient-years treatment across renal and oncology indications
- Epoetin Hospira drug substance uses same cell line, growth medium and purification as Retacrit
- BLA for Epoetin Hospira stand-alone US program

Epoetin Hospira Development Follows Step-Wise Approach



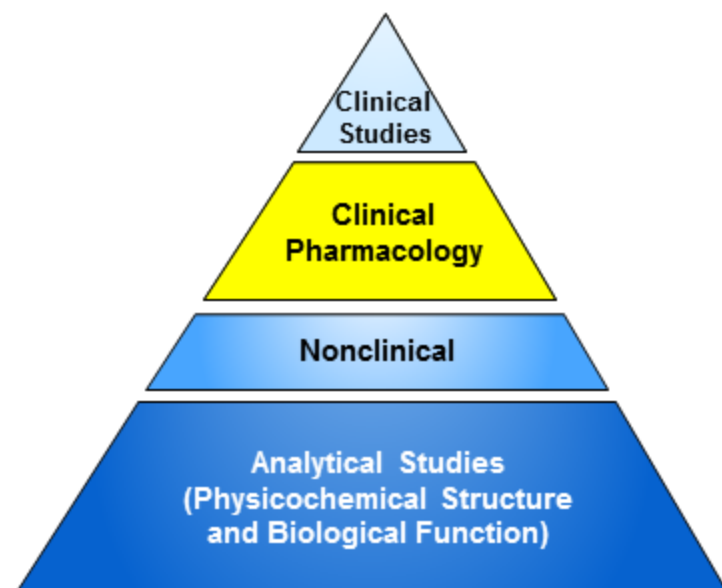
Comparative Analytical and Nonclinical Studies

- Characterization of structure, physicochemical properties and biological function
- Two comparative animal toxicology studies
 - Rat (SC administration)
 - Dog (IV administration)



Comparative Clinical Studies

- Two comparative PK/PD studies with SC administration
 - Single and multiple dose
- Two double-blind, randomized, controlled comparative safety and efficacy studies
 - SC and IV administration



Scientific Considerations for Extrapolation Across All Indications

**MoA in each
condition of use**

PK and biodistribution

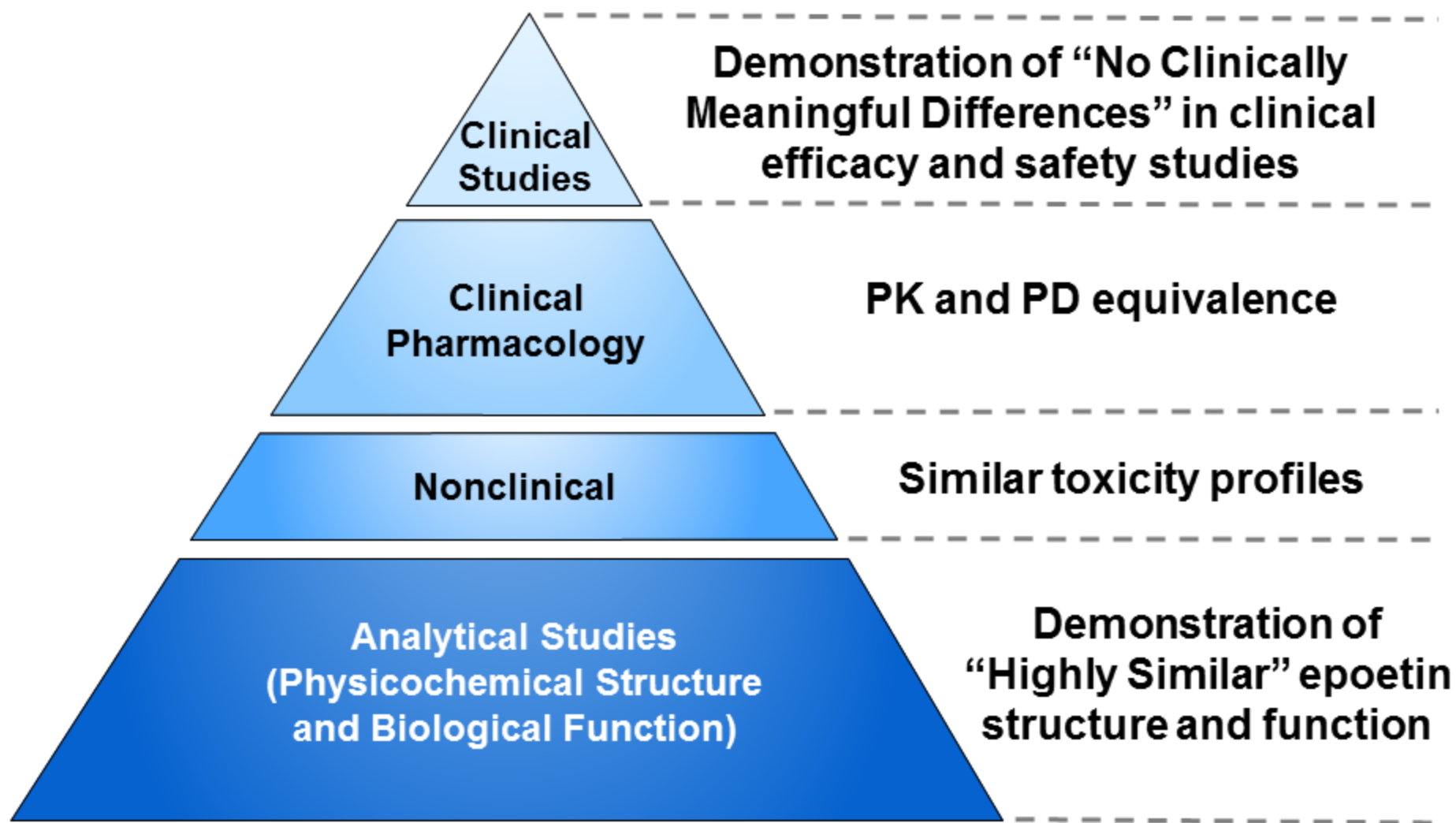
Immunogenicity

Expected toxicities

**Additional considerations
(efficacy and safety)**

- Historical studies and extensive knowledge of reference product, Epogen/Procrit, across all indications
- Totality of evidence demonstrating biosimilarity

Totality of Evidence Supports Biosimilarity to Epogen/Procrit Across All Indications



Agenda

Analytical Biosimilarity Assessment

Thomas Vanden Boom, PhD

VP, Biosimilars Pharmaceutical Sciences
Pfizer World Wide Research and
Development

Nonclinical, Clinical Pharmacology and Clinical Biosimilarity Assessment

Nancy Martin, MD, PharmD, FCP

Consultant, previously
VP Clinical Development, Biosimilars
Hospira, A Pfizer Company

Conclusion Supporting Biosimilarity and Extrapolation Across All Indications

Sumant Ramachandra, MD, PhD

External Responders

- **Paul Cornes, MD**
Clinical Oncologist
Comparative Outcomes Group, UK
- **Professor Jeffrey Crawford, MD**
Medical Oncologist
Duke Cancer Institute
- **Steven Fishbane, MD**
Nephrologist
Hofstra Northwell School of Medicine
- **Professor Wolfgang Jelkmann, MD**
Physiologist (ret.)
Universität zu Lübeck
- **Professor Iain Macdougall, MD**
Nephrologist
King's College Hospital, London
- **Professor George Rodgers, MD**
Hematologist/Oncologist
University of Utah
- **Professor Jerry Spivak, MD**
Hematologist
Johns Hopkins University Hospital
- **Jay Wish, MD**
Nephrologist
Indiana University Health

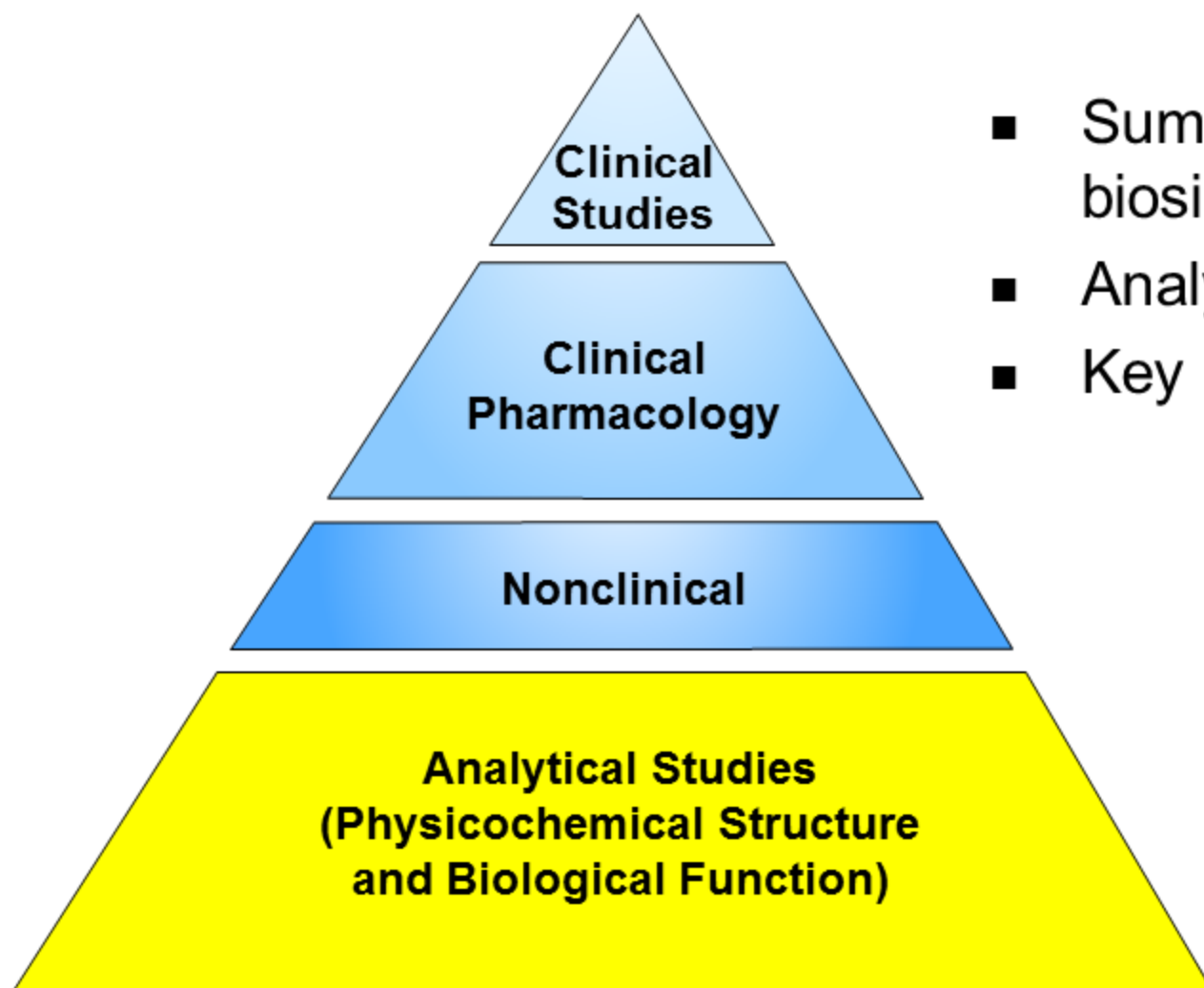
Analytical Biosimilarity Assessment

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VP, Biosimilars Pharmaceutical Sciences

Pfizer World Wide Research and Development

Comprehensive Analytical Studies Provide Foundation for Biosimilarity Assessment



- Summary of product lots used in biosimilarity assessment
- Analytical methods
- Key results

Significant Number of Lots Used in Analytical Biosimilarity Assessment

Product	Description	Number of Lots
Epogen/Procrit	Drug product	54
Epoetin Hospira	Drug substance	9
	Drug product	35

- All dose strengths included in assessment
- Impact of product age evaluated across shelf life of products

Wide Range of Analytical Methods Used to Assess Similarity

Primary Structure

- Trypsin Peptide Map (RP-UPLC-MS)
 - Amino Acid Sequence
 - Disulfide Mapping
 - Sites of Post-Translational Modification
- De-N-Glycosylated Intact Mass (LC-MS)
- Free Sulfhydryls (RP-HPLC)

Secondary and Tertiary Structure

- Far-UV Circular Dichroism (Far-UV CD)
- Near-UV CD
- Infrared Spectroscopy (FTIR)
- Intrinsic Fluorescence
- Differential Scanning Calorimetry (DSC)
- Hydrodynamic parameters (SV-AUC)

Post-Translational Modifications

- N-Linked Native Glycans (HILIC-UPLC)
- N-Linked Native Glycans (WAX)
- Deacetylated N-Linked Glycans (HILIC-UPLC)
- Double Enzyme Digested N-Linked Glycans (HILC-UPLC)
- O-Linked Native Glycans (Trypsin Peptide Map)
- Monosaccharides (RP-HPLC)
- Total Sialic Acids (RP-HPLC)
- Isoform Distribution (CZE)
- Alpha Gal-Gal (HPAEC-PAD)
- N-Glycan Site Occupancy (Protease Digests in H₂O¹⁸)
- Site-Specific N-Glycans (Protease Digest LC-MS)
- Glycan ID (2D WAX HILIC)

Product-Related Substances & Impurities

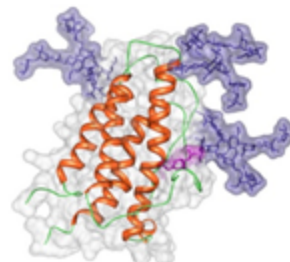
- Trypsin Peptide Map (RP-UPLC-MS)
- Oxidized Species (Lys-C, K4 Peptide)
- Quantitative Western Blot
- HMWS (SEC)
- Silver Stain SDS-PAGE
- HMWS (SV-AUC)

Drug Product Characteristics

- Epoetin Content (RP-UPLC)
- Volume, USP <1>
- Microflow Imaging
- NanoSight

Functional Activity

- *In Vivo* Normocythaemic Mouse Bioassay
- *In Vitro* Cell-Based Bioassay
- Competitive Receptor Binding
- Surface Plasmon Resonance

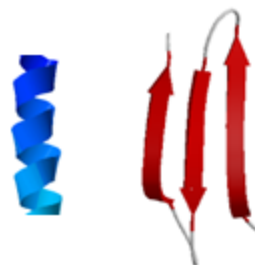


Molecular Features of Epoetin Evaluated in Analytical Studies



Primary structure

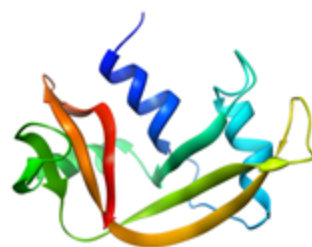
Amino acid sequence of a protein



α -helix β -sheet

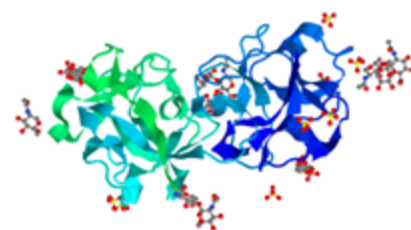
Secondary structure

Local conformations in proteins maintained by hydrogen bonds



Tertiary structure

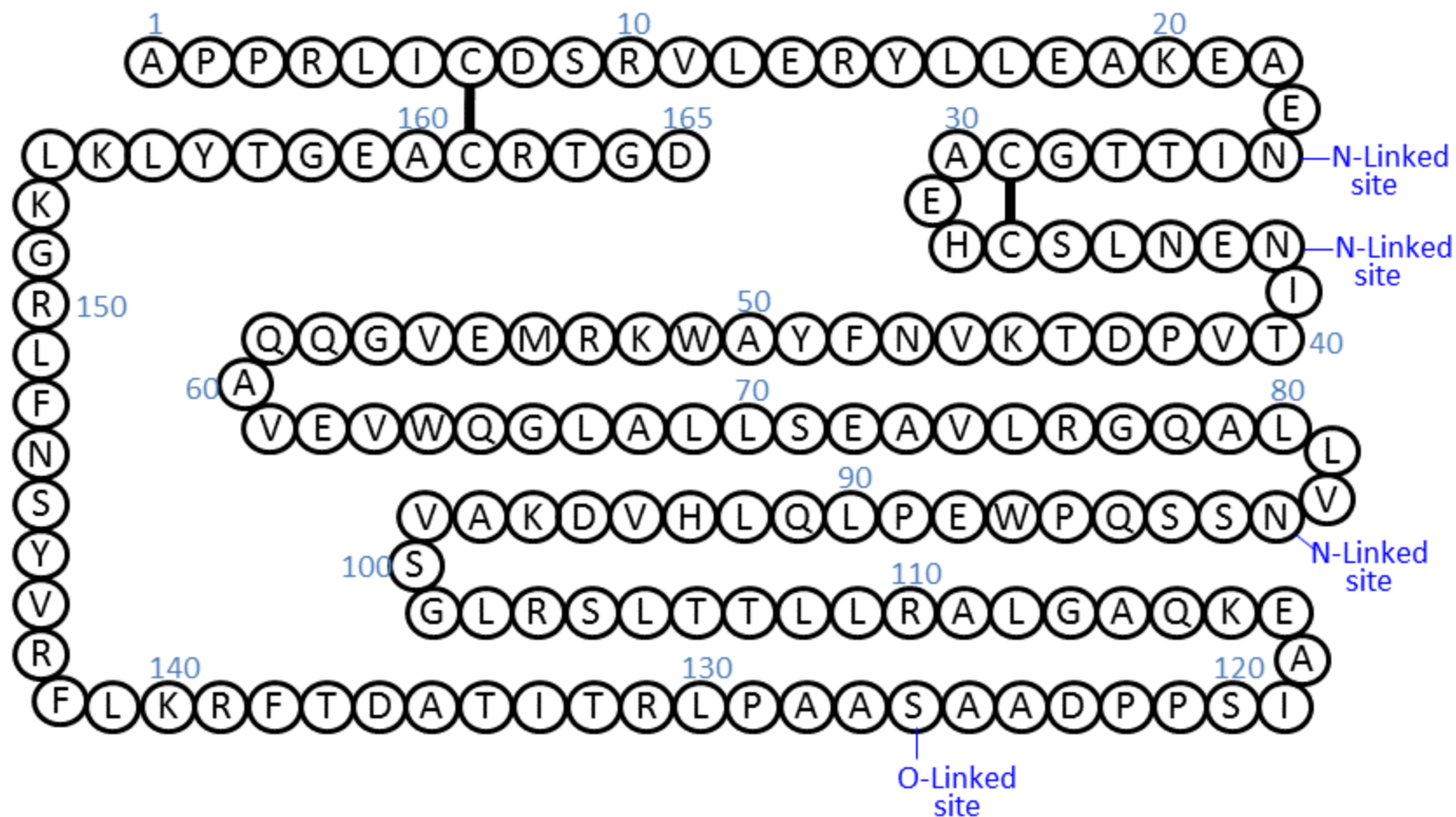
Organization of secondary structures to form the folded protein



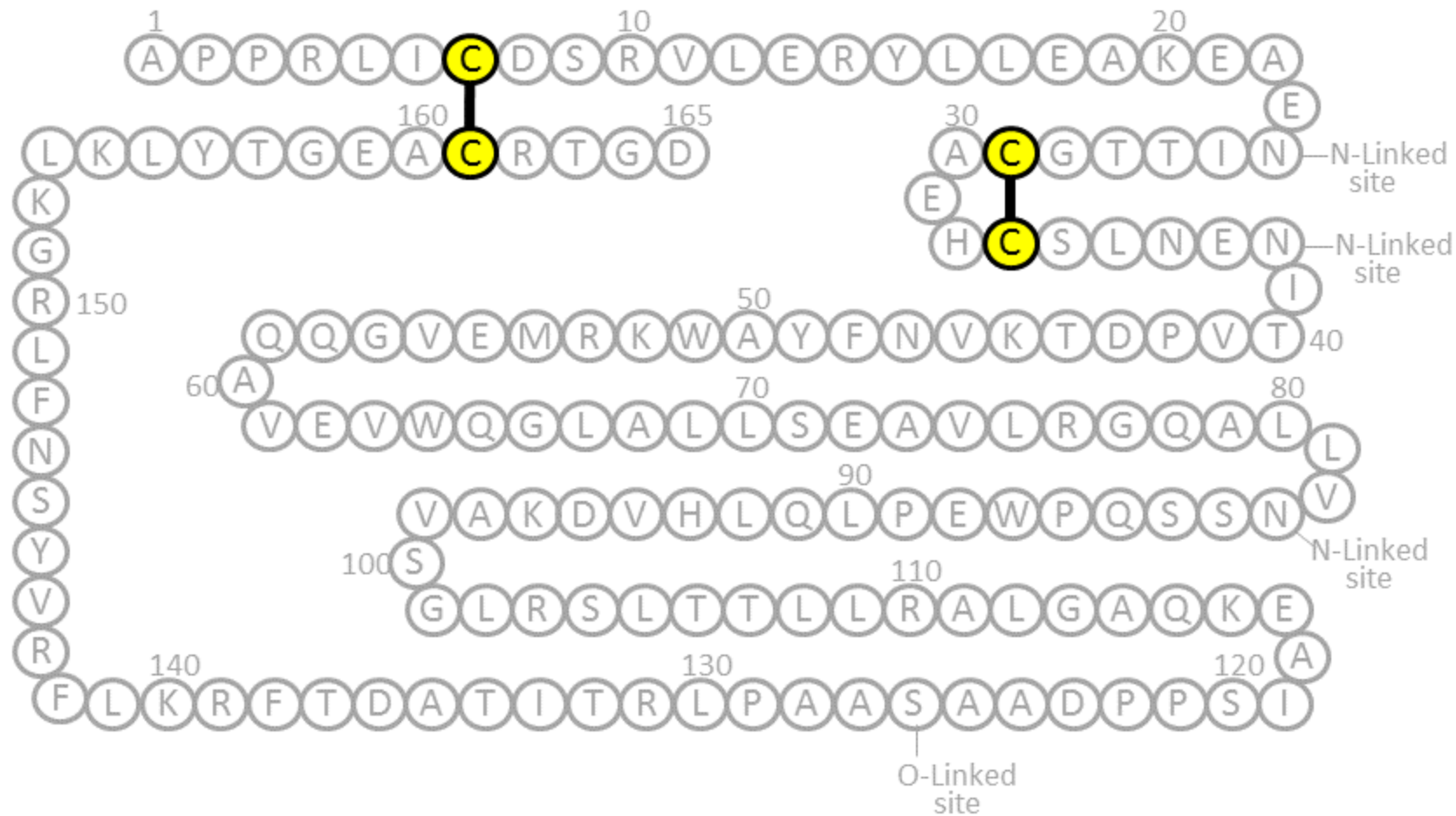
Post-translational modifications

Covalent modification of proteins, including glycosylation

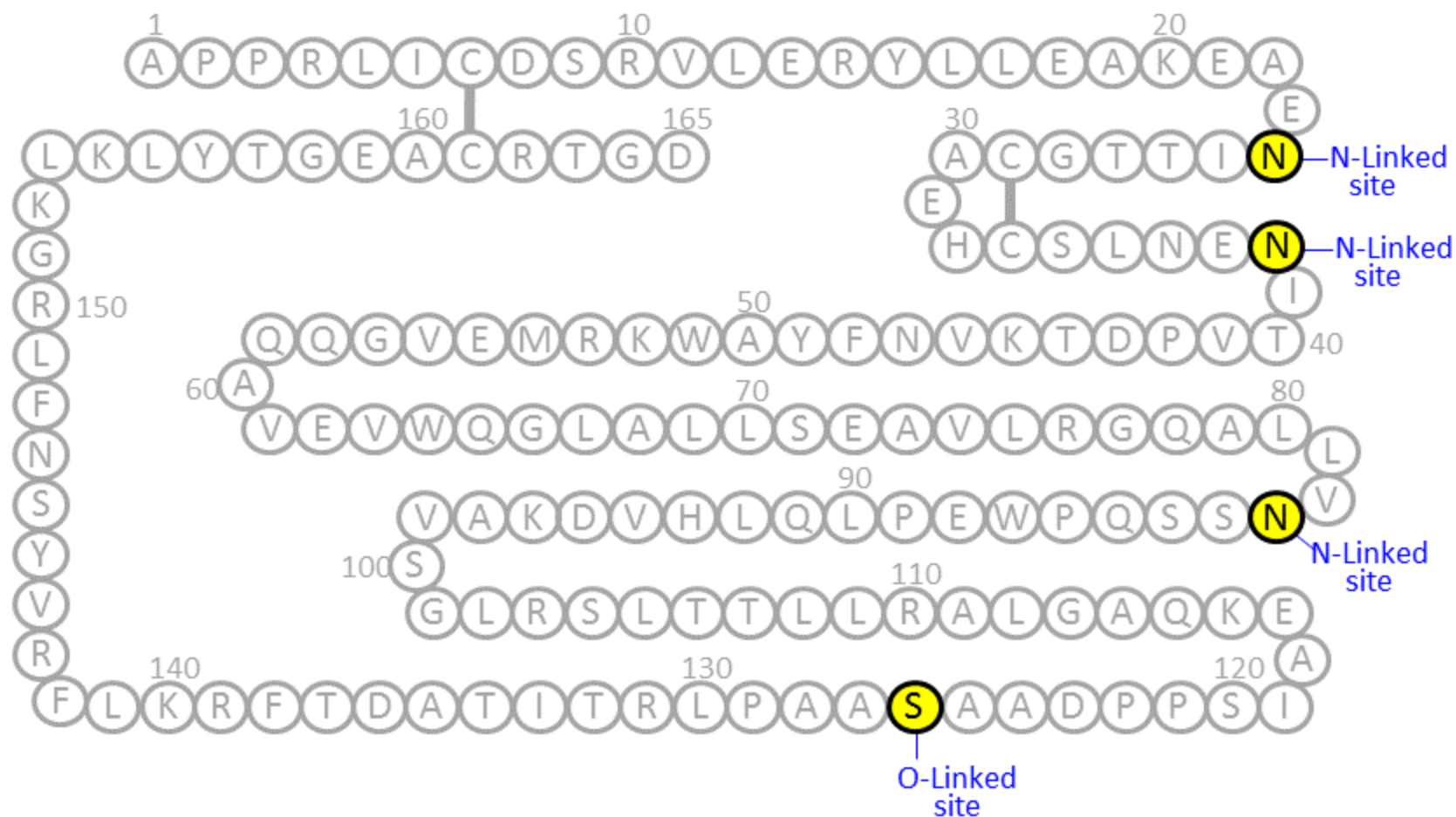
Epoetin Hospira Primary Structure Identical to Reference Product



Epoetin Hospira Disulfide Linkages Identical to Reference Product



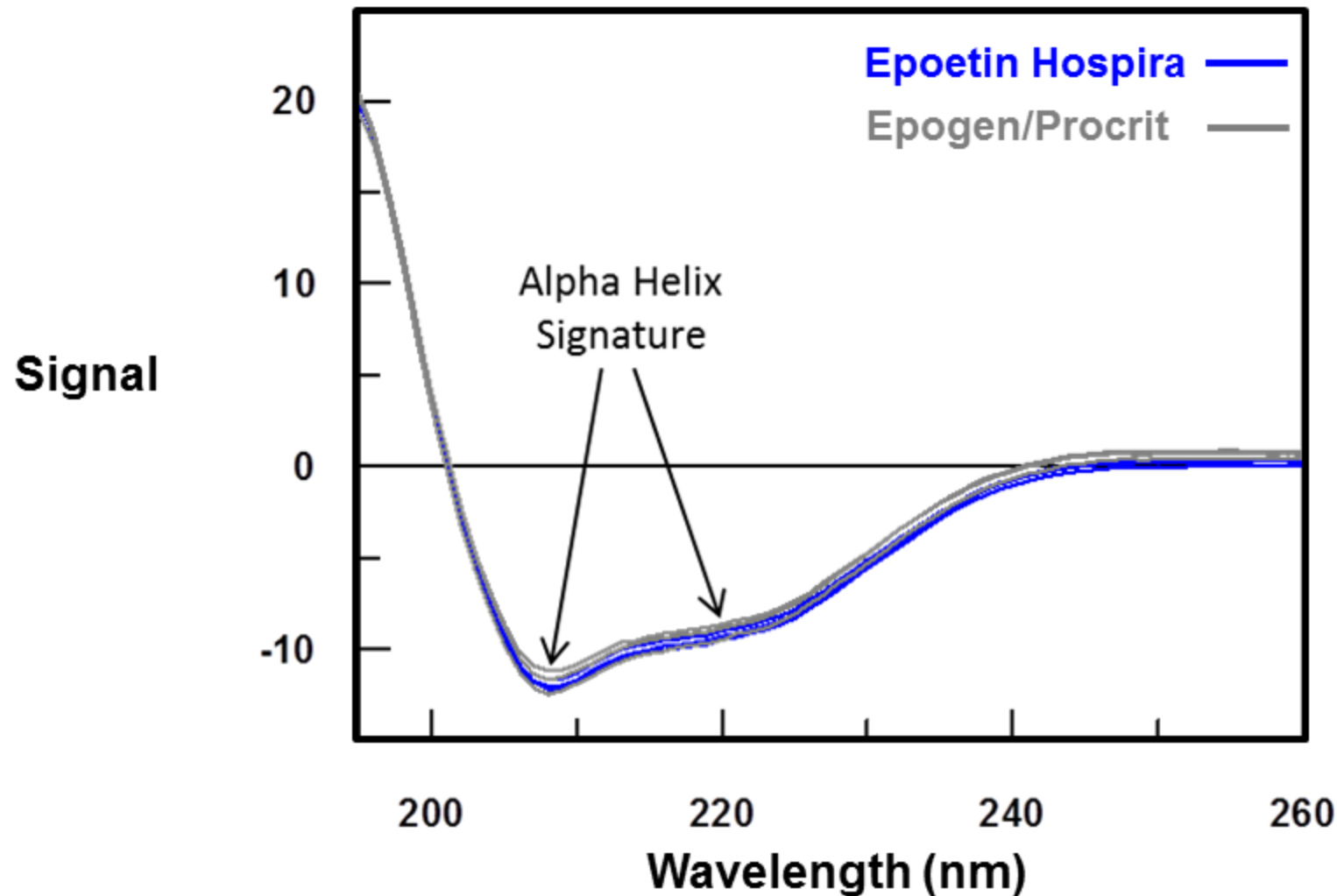
Epoetin Hospira Glycosylation Sites Identical to Reference Product



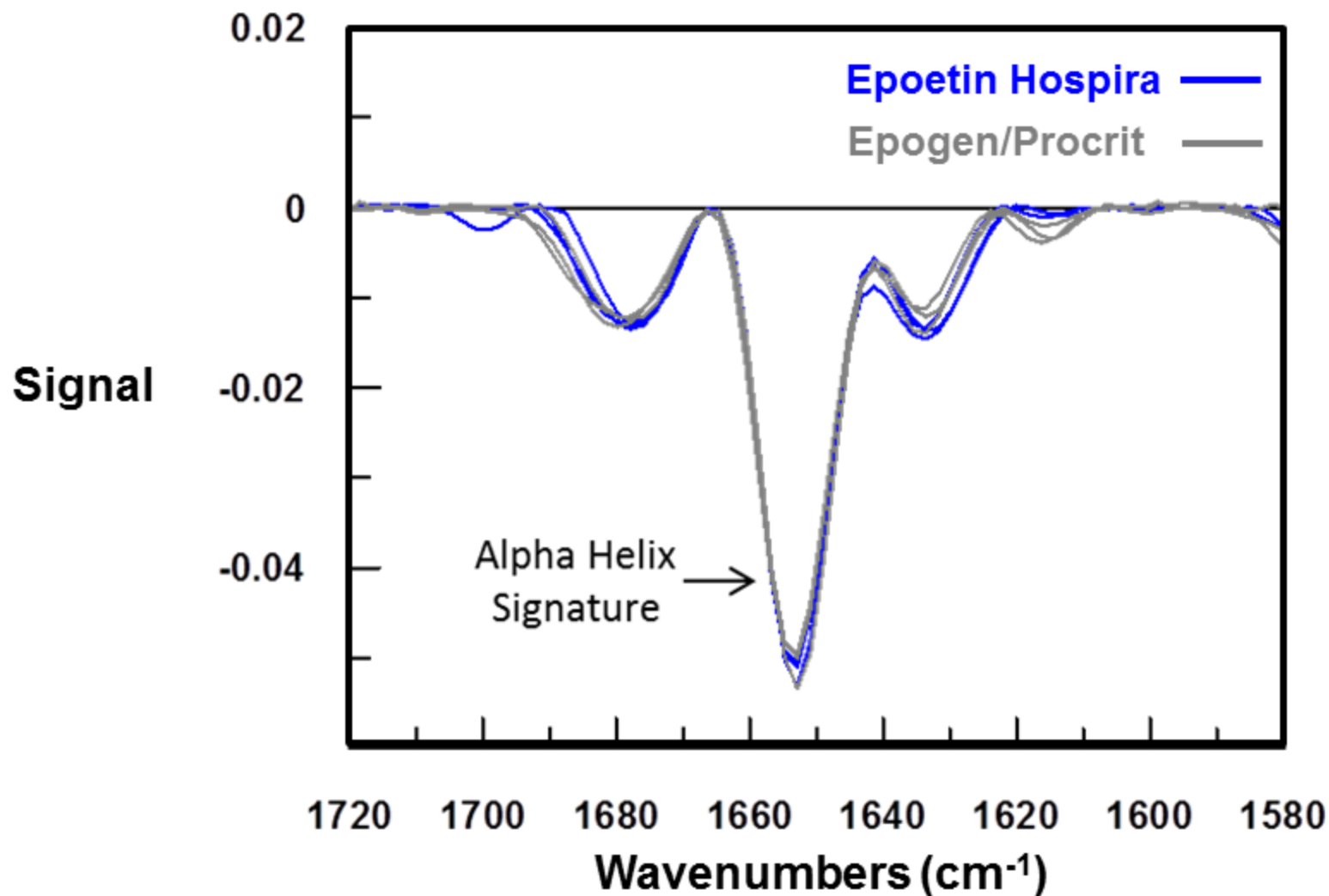
Higher Order Structure Examined Using Complementary Spectral Methods

Attribute	Test Method	Measurement
Secondary structure	Far-UV Circular Dichroism (CD)	Relative percentage of α -helix, β -sheet and random coil secondary structures
	Fourier-Transform Infrared Spectroscopy (FTIR)	IR absorption bands associated with amide linkages between amino acids in protein backbone
Tertiary structure	Near-UV Circular Dichroism (CD)	Microenvironments of tryptophan, tyrosine and phenylalanine residues

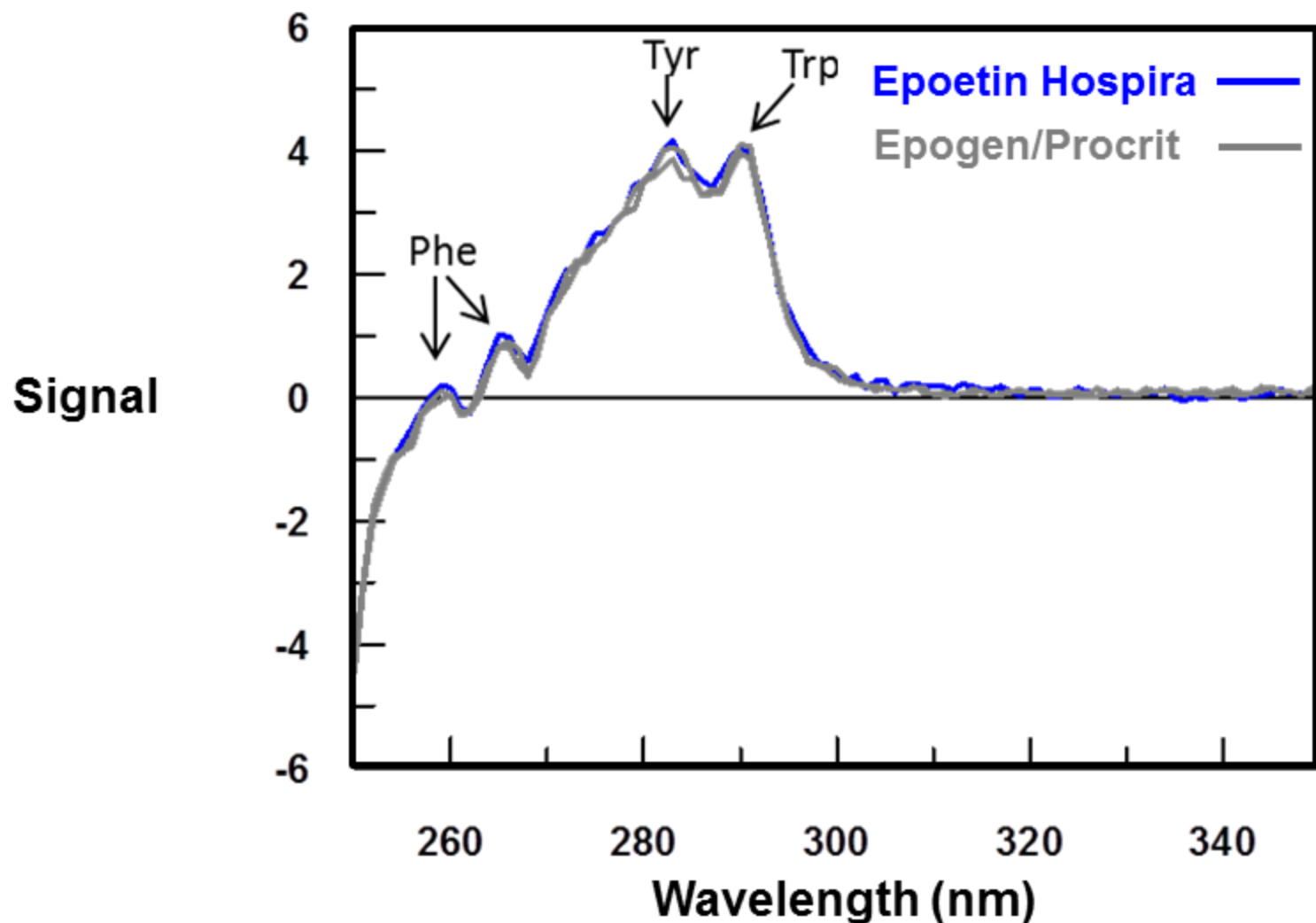
Far-UV CD Measure of Secondary Structure Similar to Reference Product



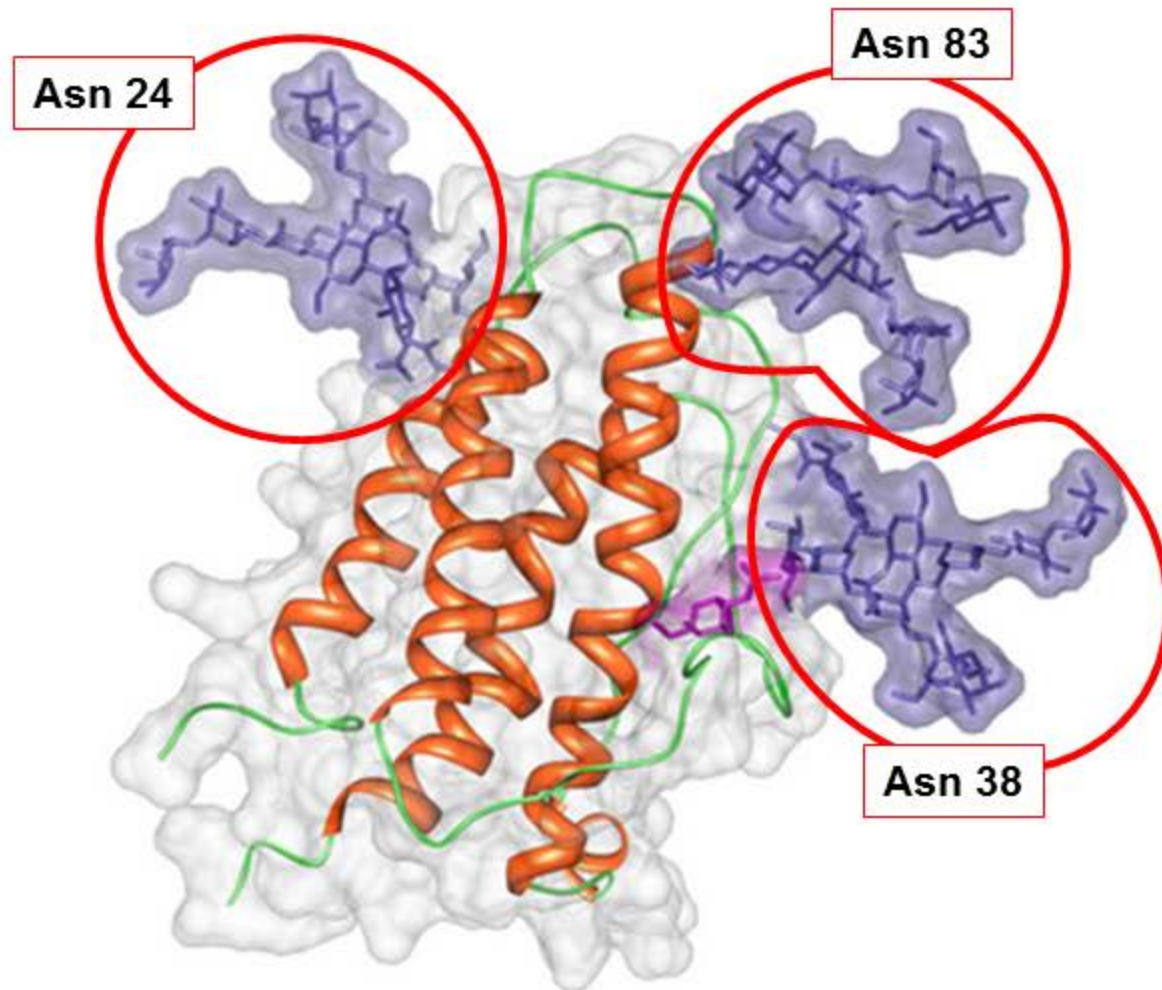
FTIR Measure of Secondary Structure Also Similar to Reference Product



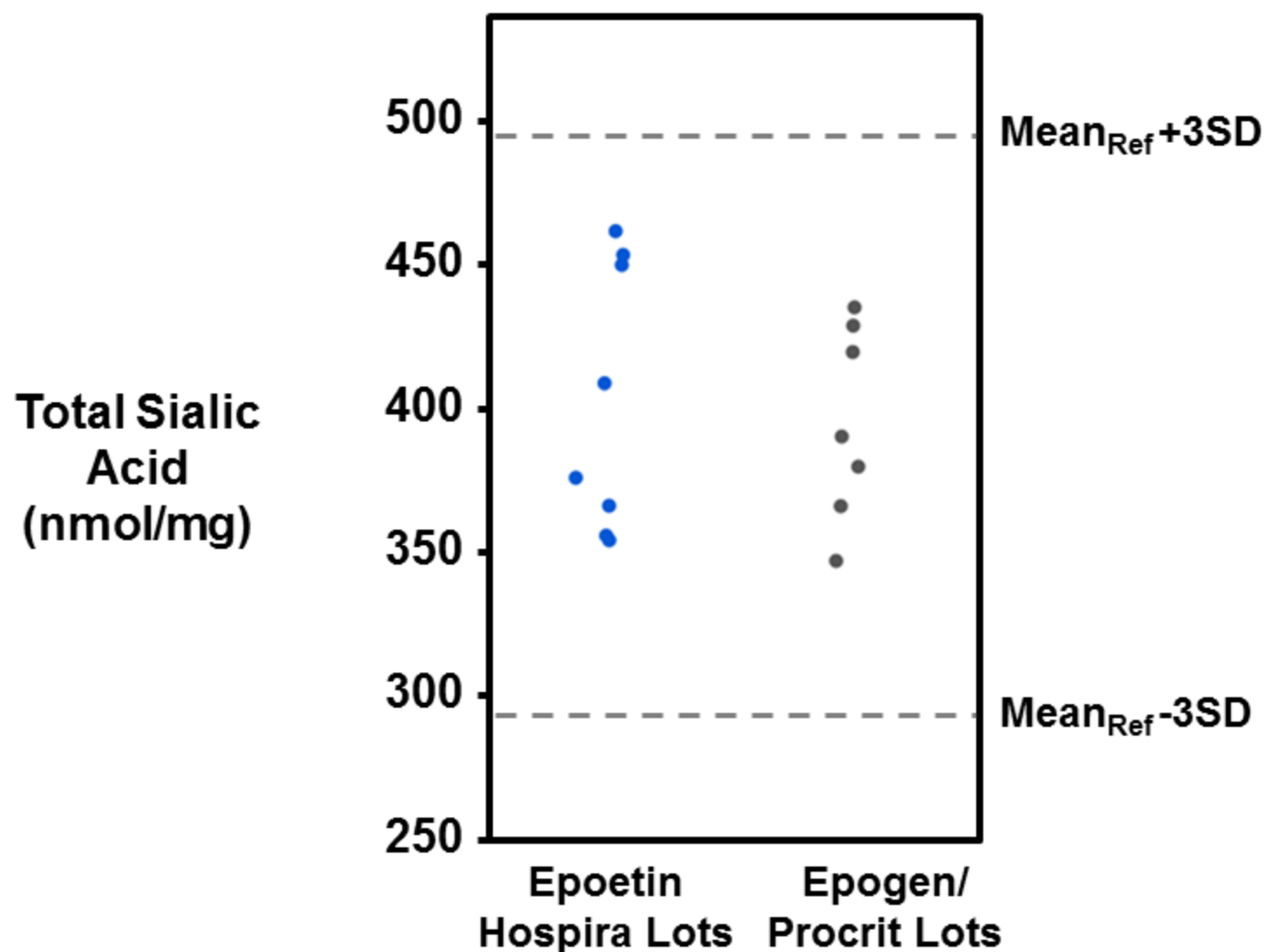
Near-UV CD Spectra Measure of Tertiary Structure Similar Between Products



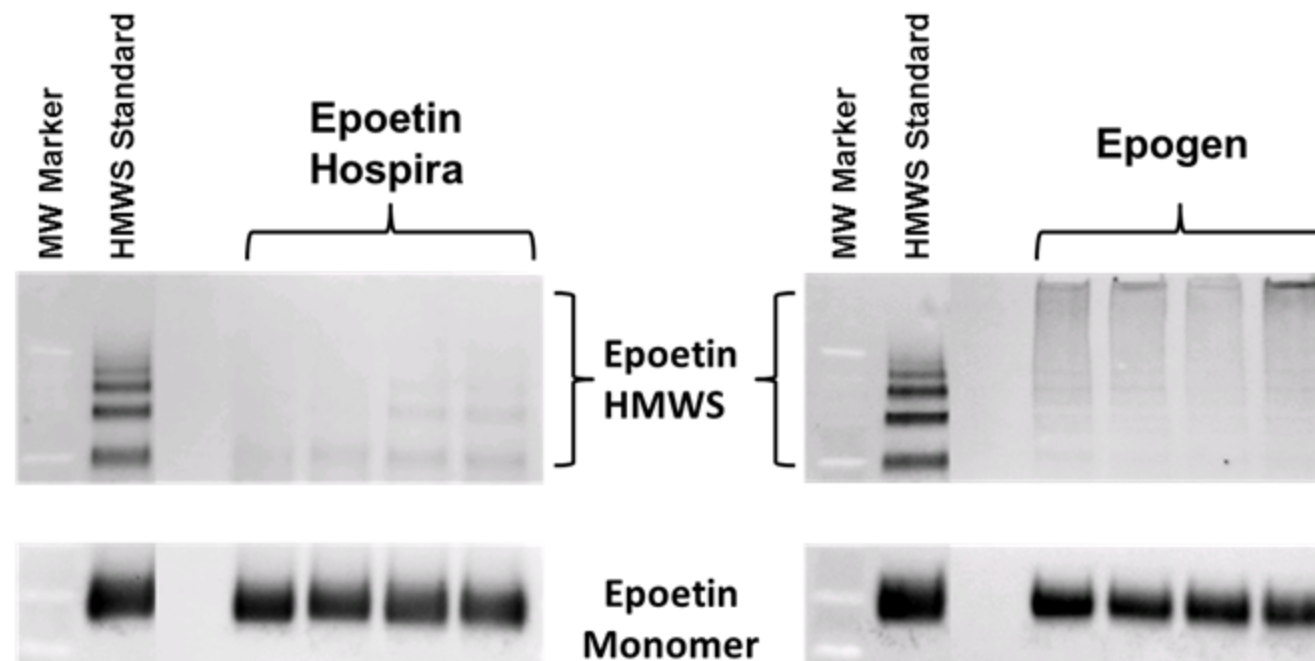
Epoetin Highly Glycosylated Protein



Total Sialic Acid Similar Between Epoetin Hospira and Epogen/Procrit



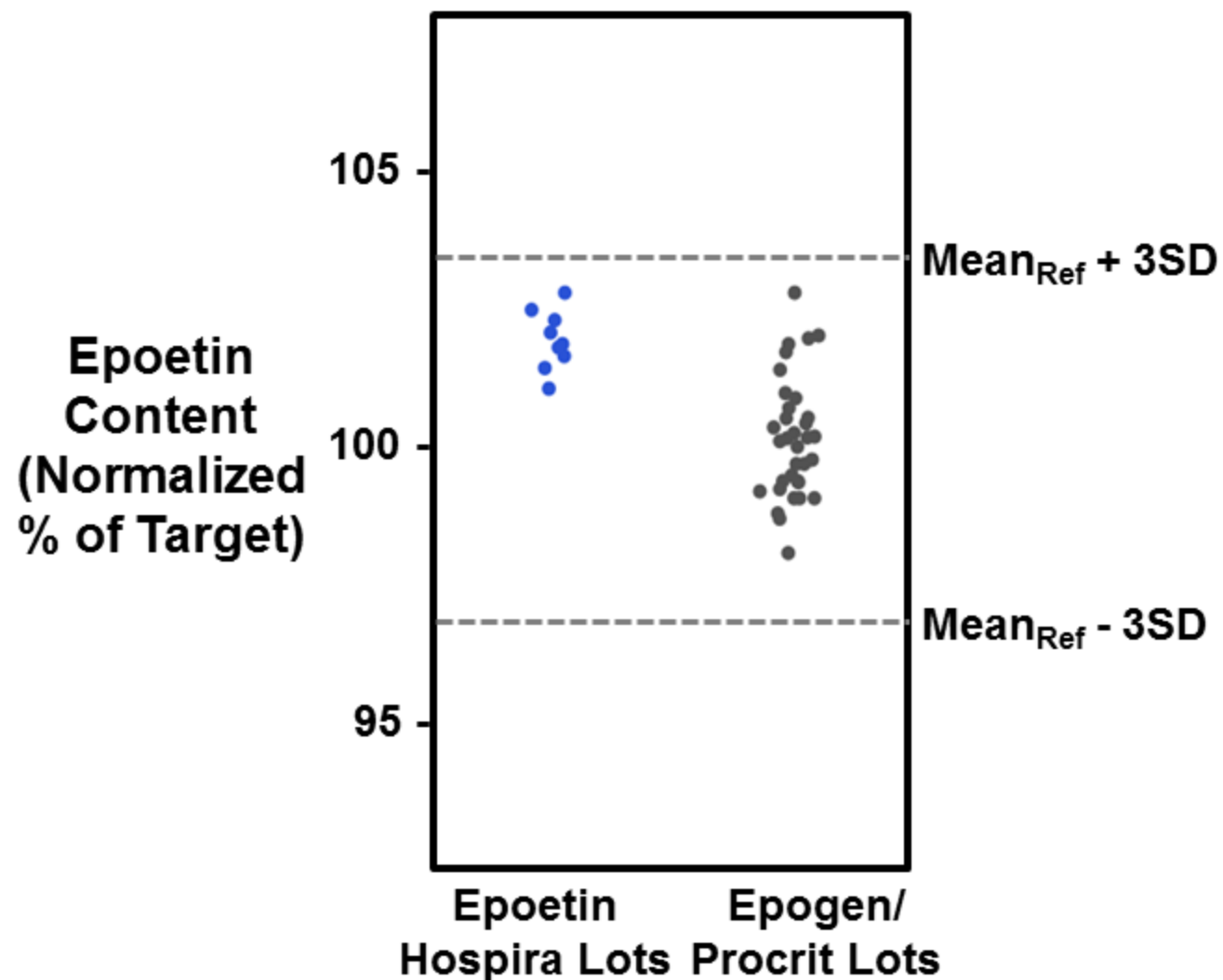
Epoetin Hospira High Molecular Weight Species (HMWS) at or Below Levels in Reference Product



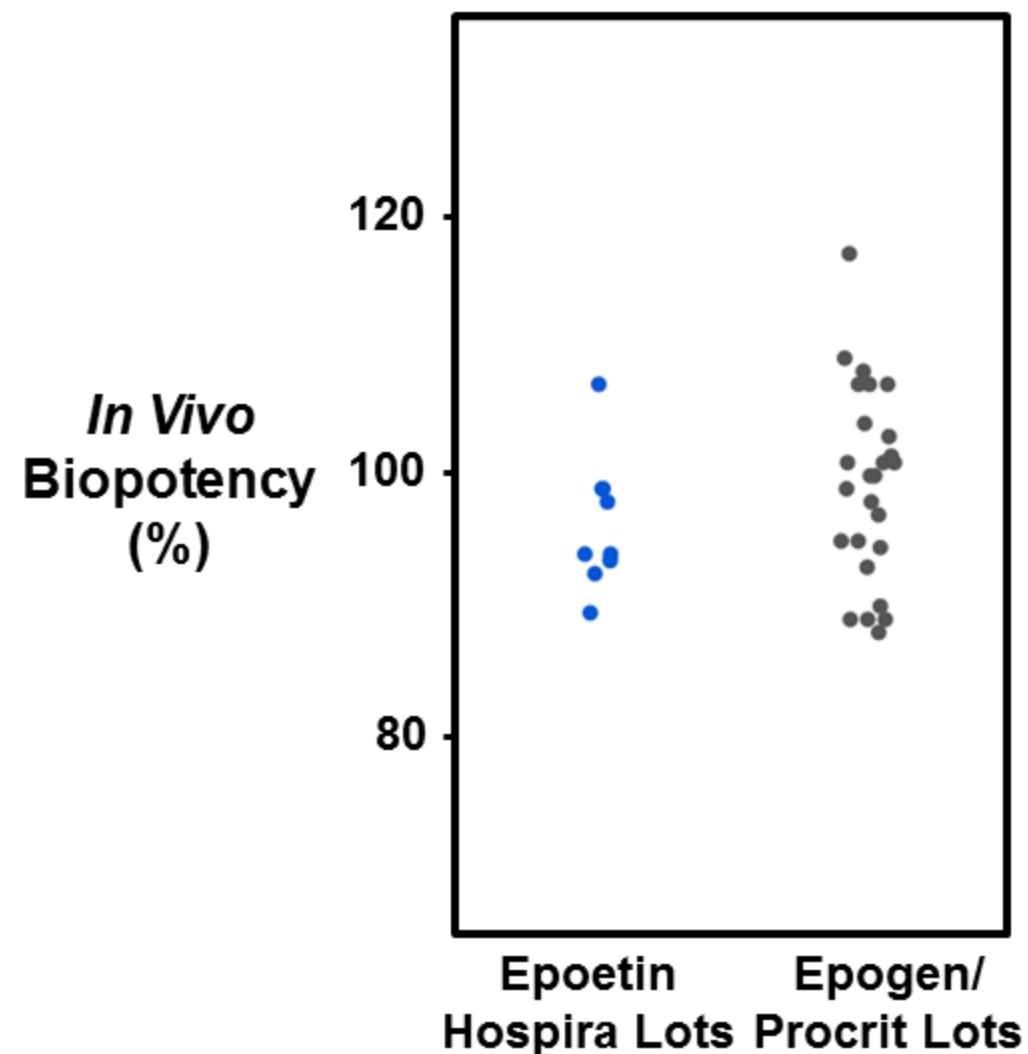
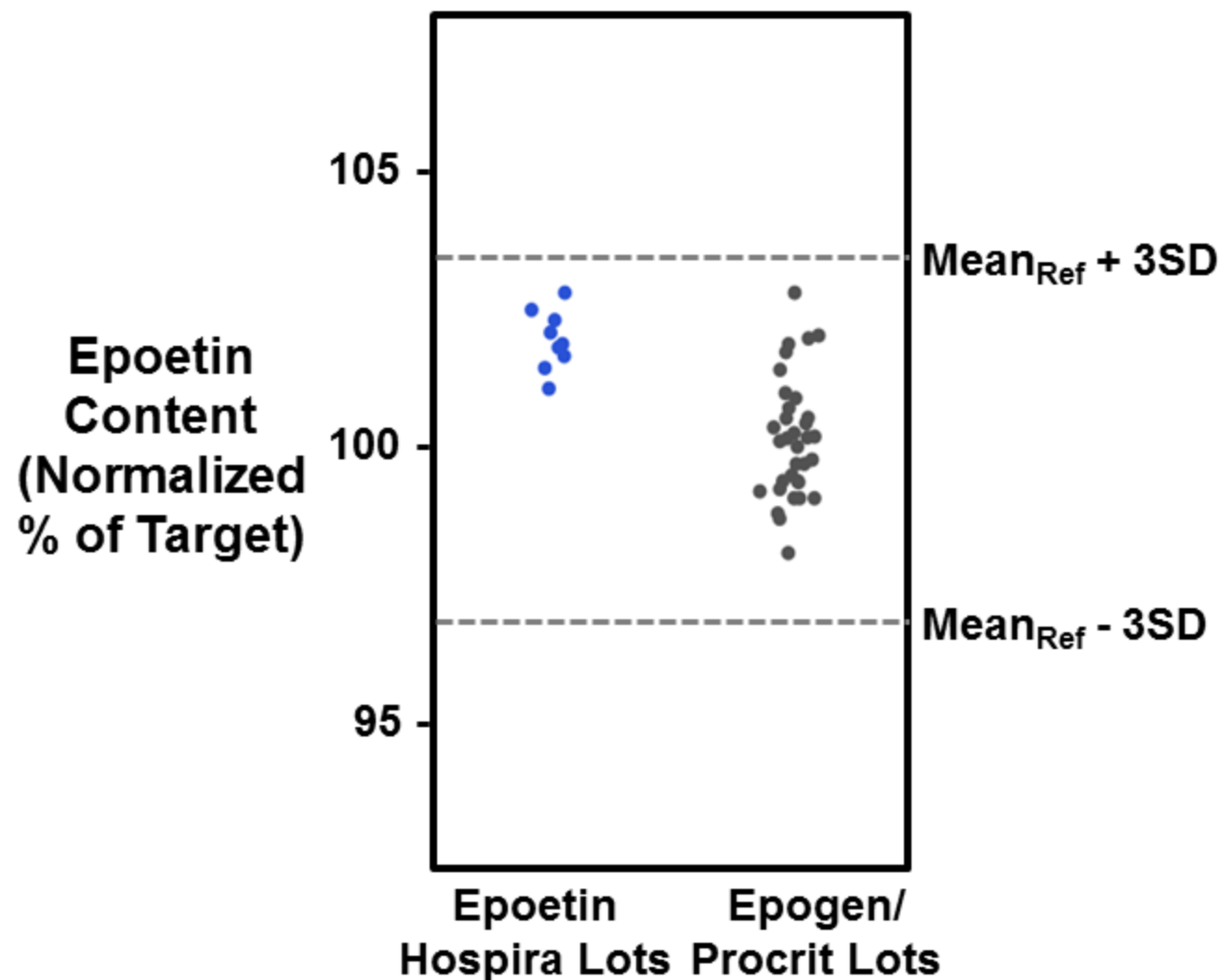
Product	Mean	Standard Deviation	Minimum	Maximum	No. of Lots Tested
Epoetin Hospira	0.4%	0.0%	0.4%	0.4%	22
Epogen/Procrit	0.5%	0.1%	0.4%	0.7%	14

Note: Values for all lots of Epoetin Hospira tested were below the method LOQ (0.4%) and were assigned a value of 0.4% for the quantitative comparative analysis

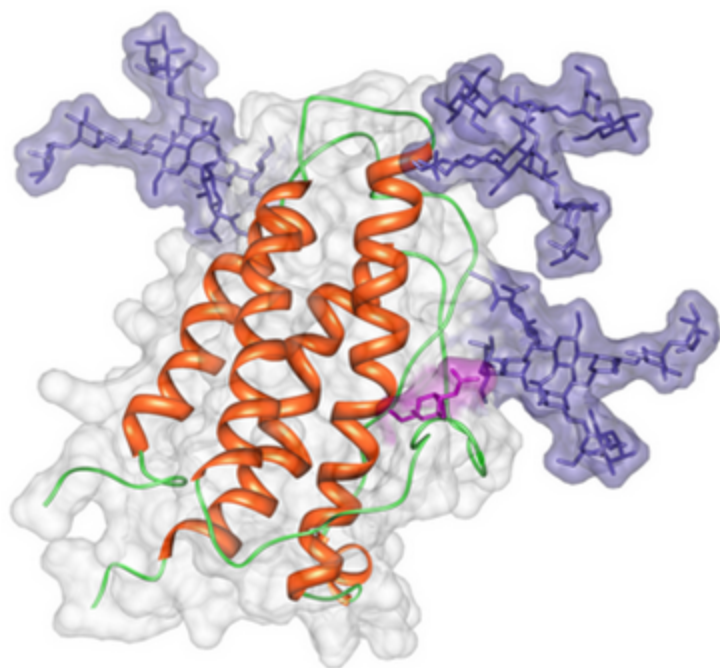
Epoetin Content Highly Similar to Epogen/Procrit Reference Product



Epoetin Content Highly Similar to Epogen/Procrit Reference Product

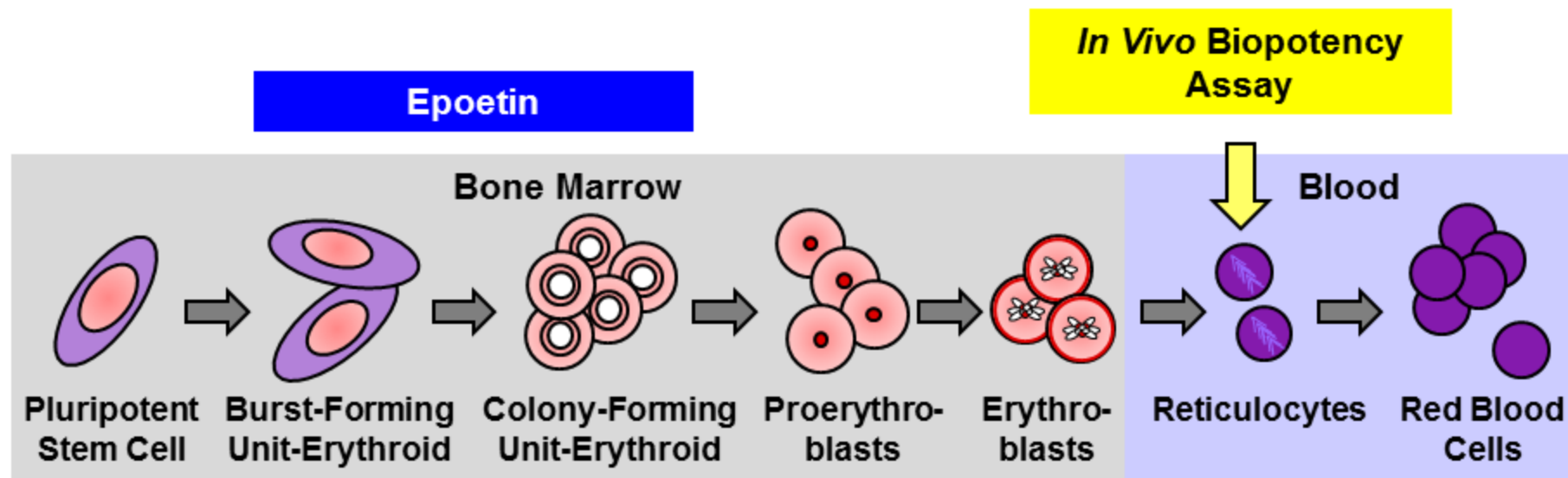


Functional Activity Evaluated Using Multiple Complementary Methods



- *In vivo* biopotency
- *In vitro* cell-based biopotency
- Receptor binding
- Receptor binding kinetics using SPR

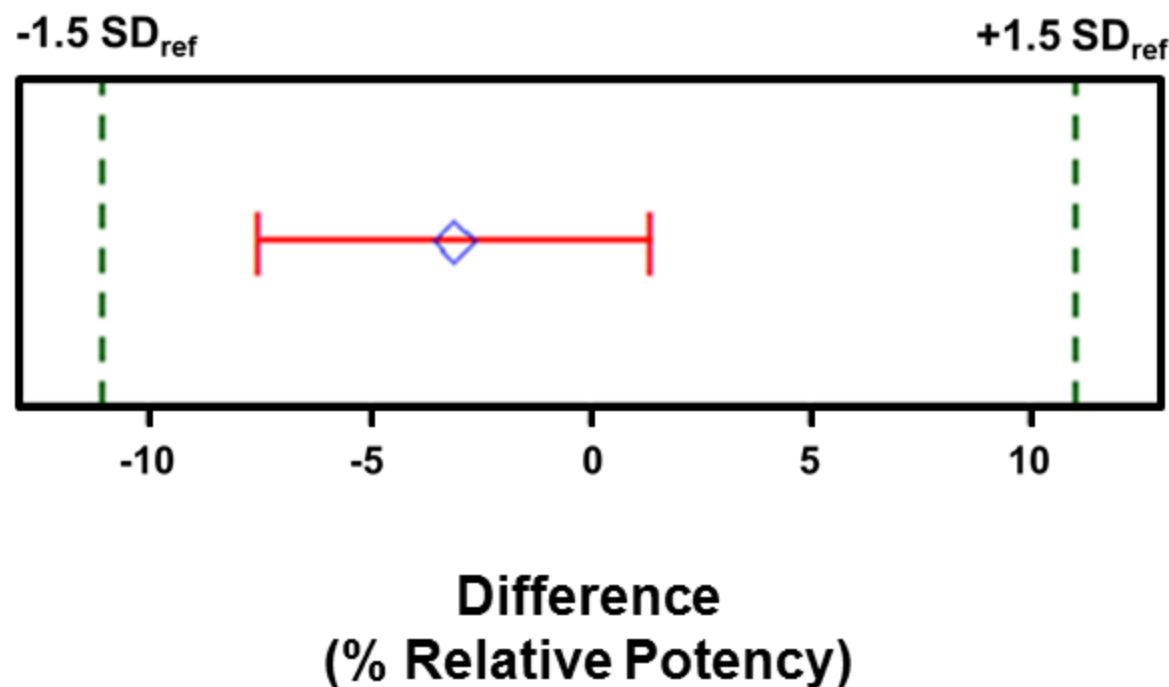
In Vivo Biopotency Provides Clinically Relevant Functional Measure



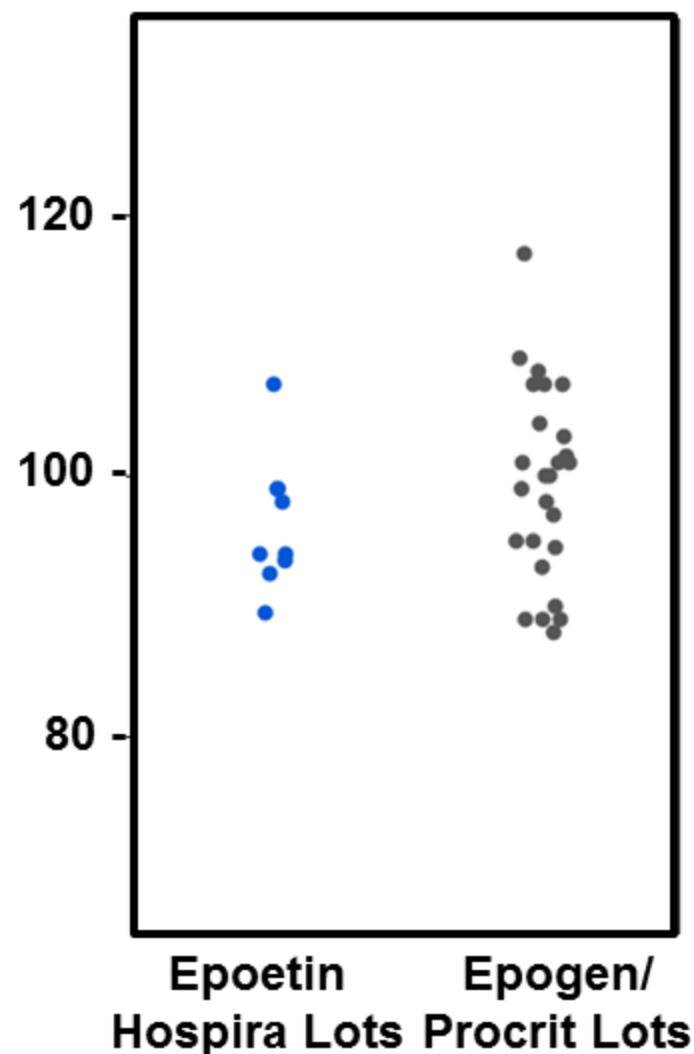
- Measures number of reticulocytes in peripheral blood
- Same measure used in clinical studies

Equivalence Demonstrated Between Products for *In Vivo* Biopotency

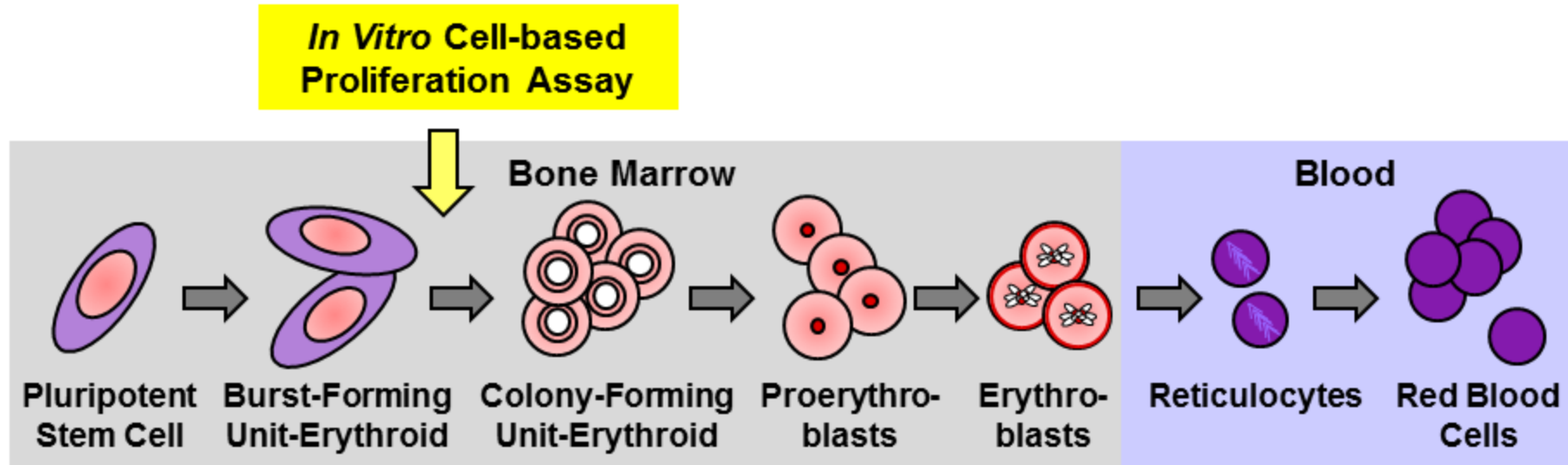
Mean Difference (Epoetin Hospira – Reference)
with 90% CI and Equivalence Bounds



In Vivo
Biopotency
(%)

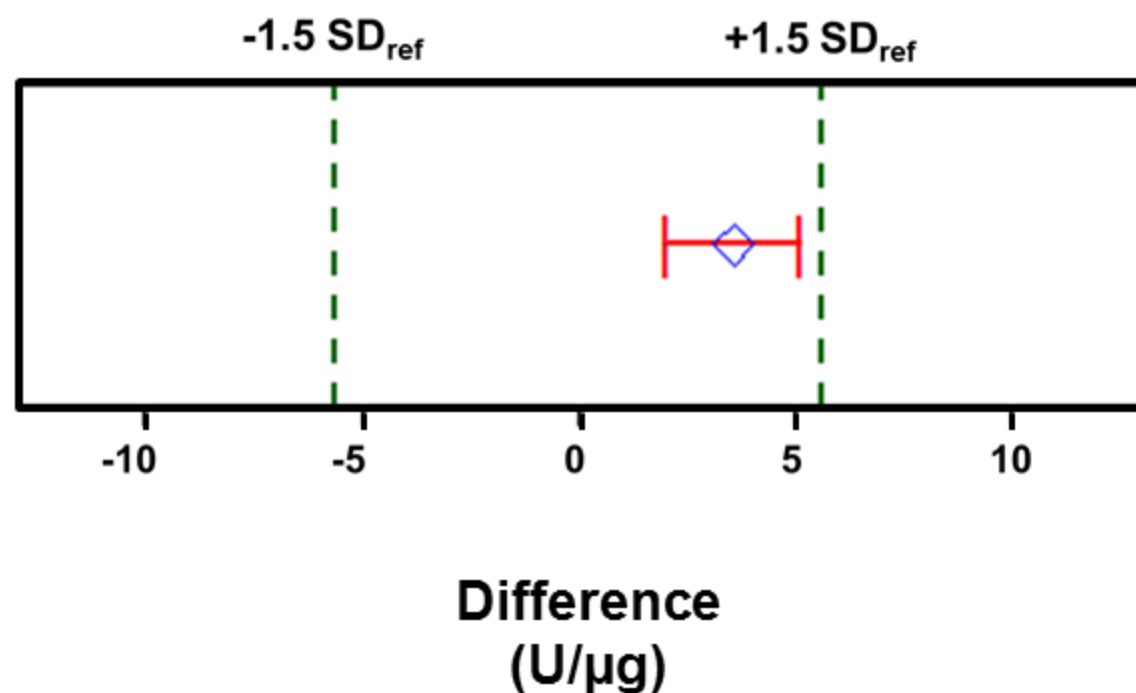


In Vitro Cell-Based Assay Measures Epoetin-Dependent Proliferation of Cell Line Analogous to Initiation of RBC Maturation Cascade

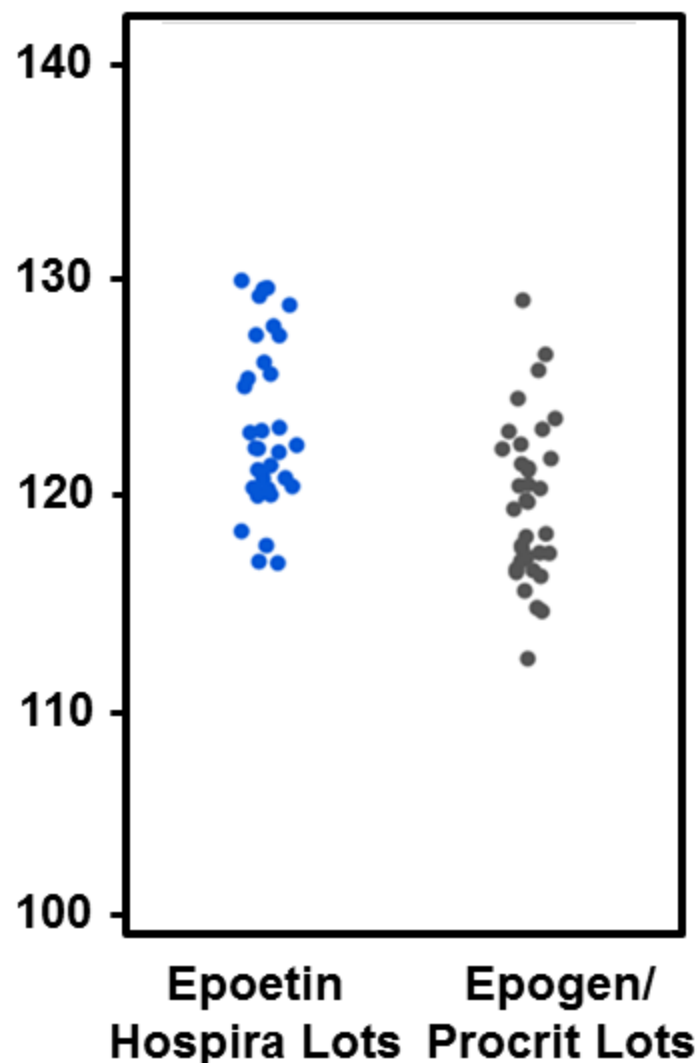


Equivalence Demonstrated for *In Vitro* Cell-Based Specific Activity

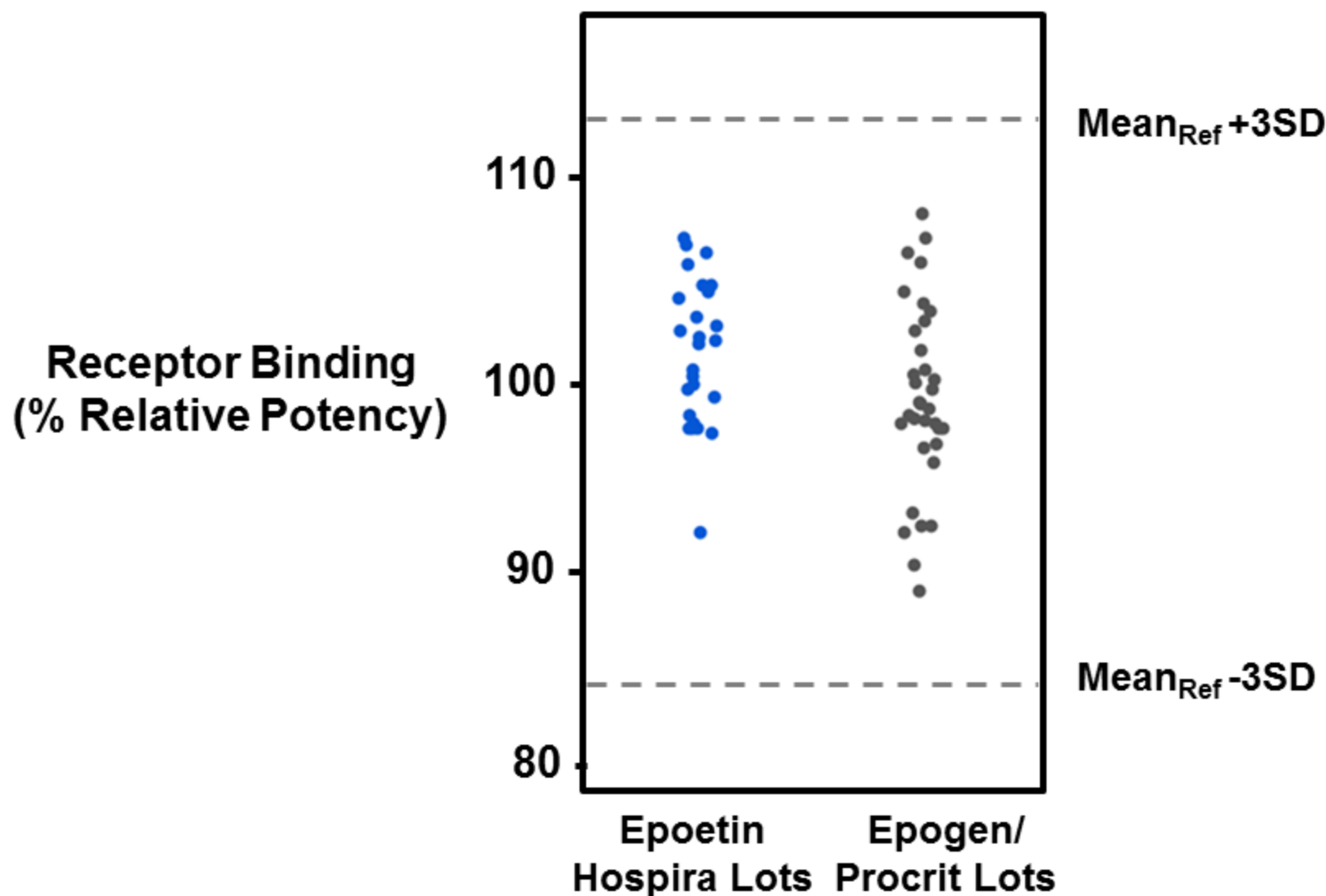
Mean Difference (Epoetin Hospira – Reference)
with 90% CI and Equivalence Bounds



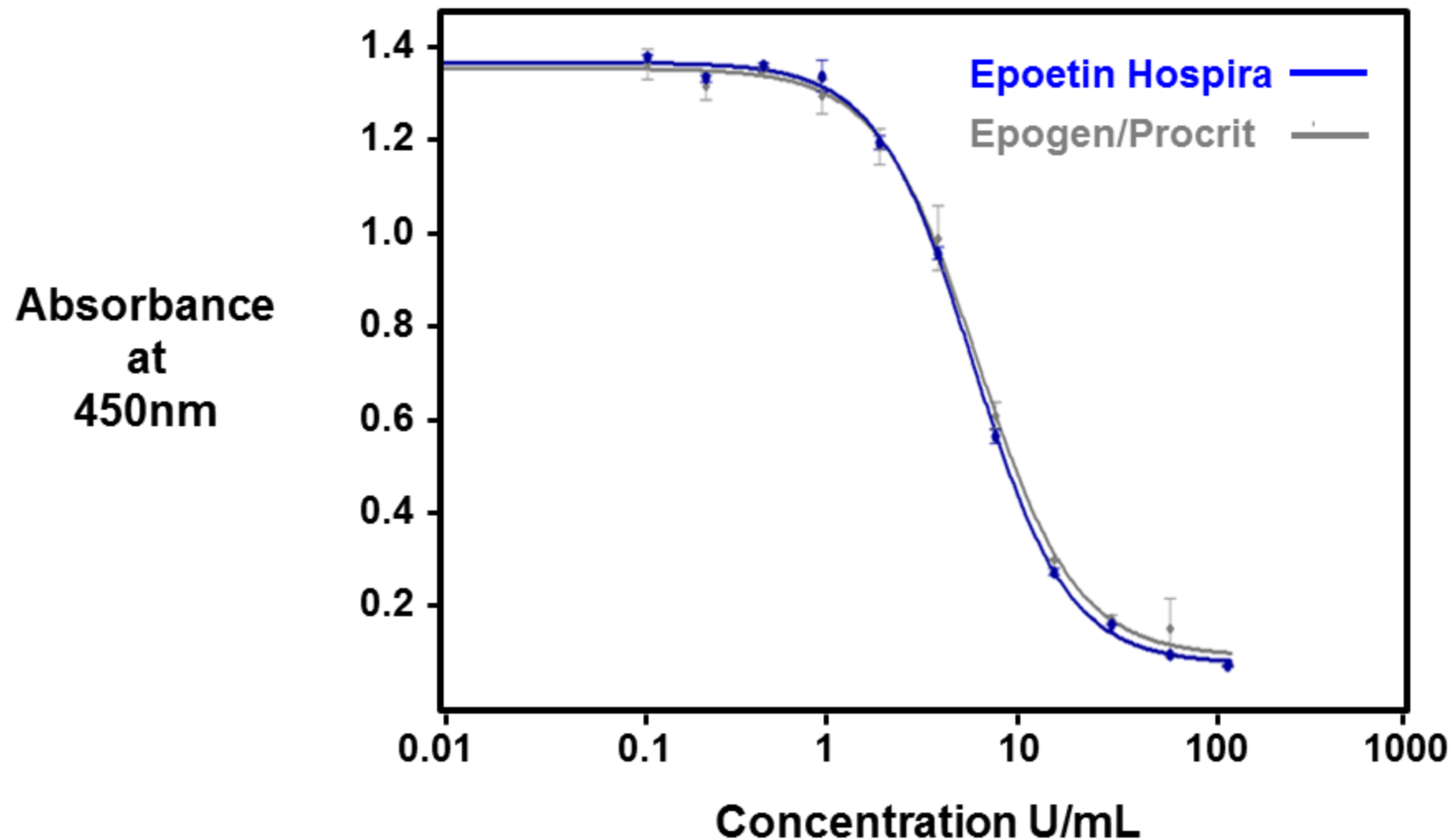
In Vitro
Cell-Based
Specific
Activity
(U/μg)



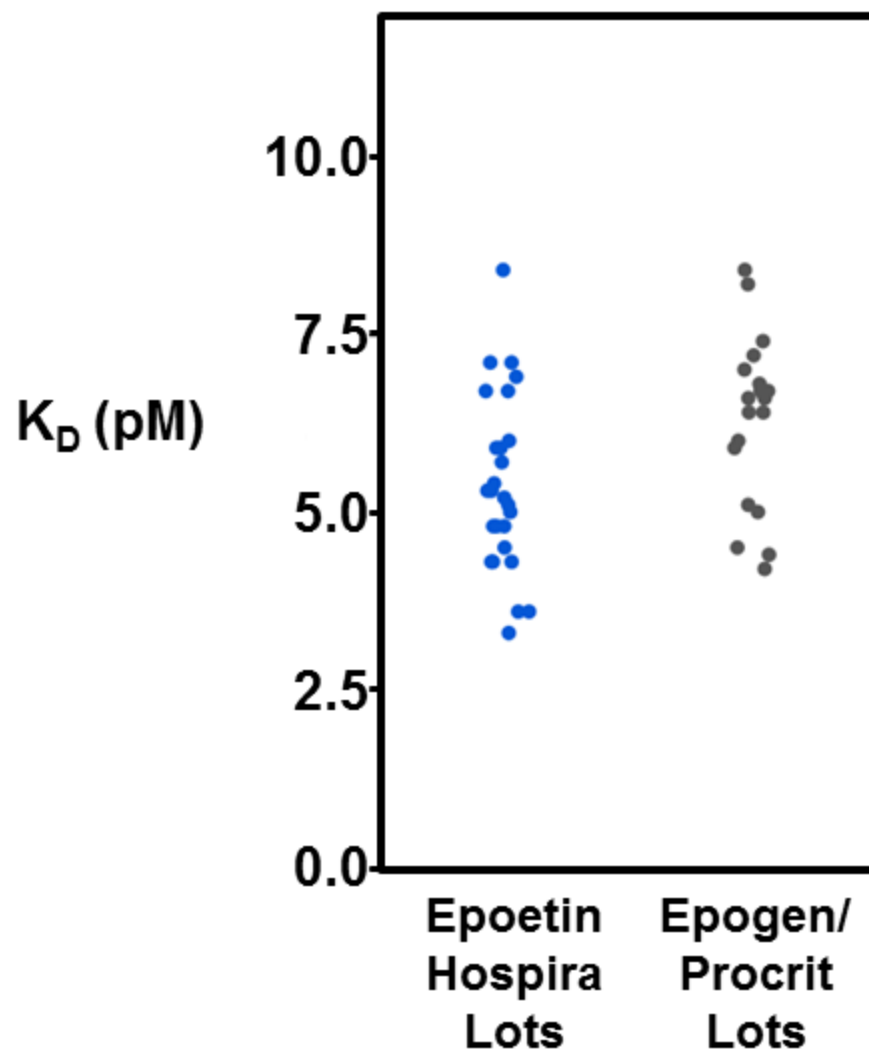
Epoetin Receptor Binding Similar Between Products



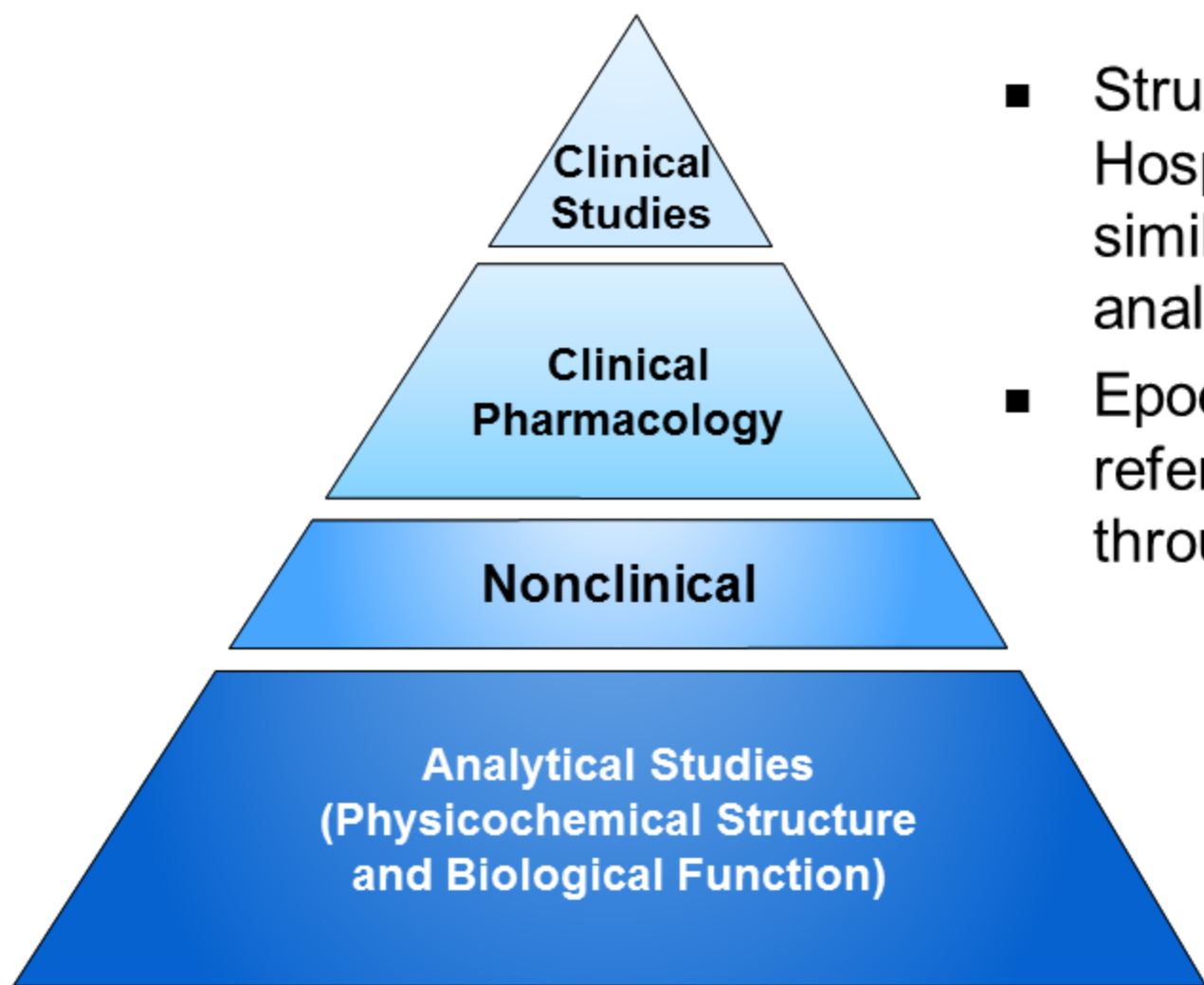
Receptor Binding Dose Response Curve Consistent Across Products



Receptor Binding Affinity Similar Between Products



Epoetin Hospira is Analytically Highly Similar to Epogen/Procrit

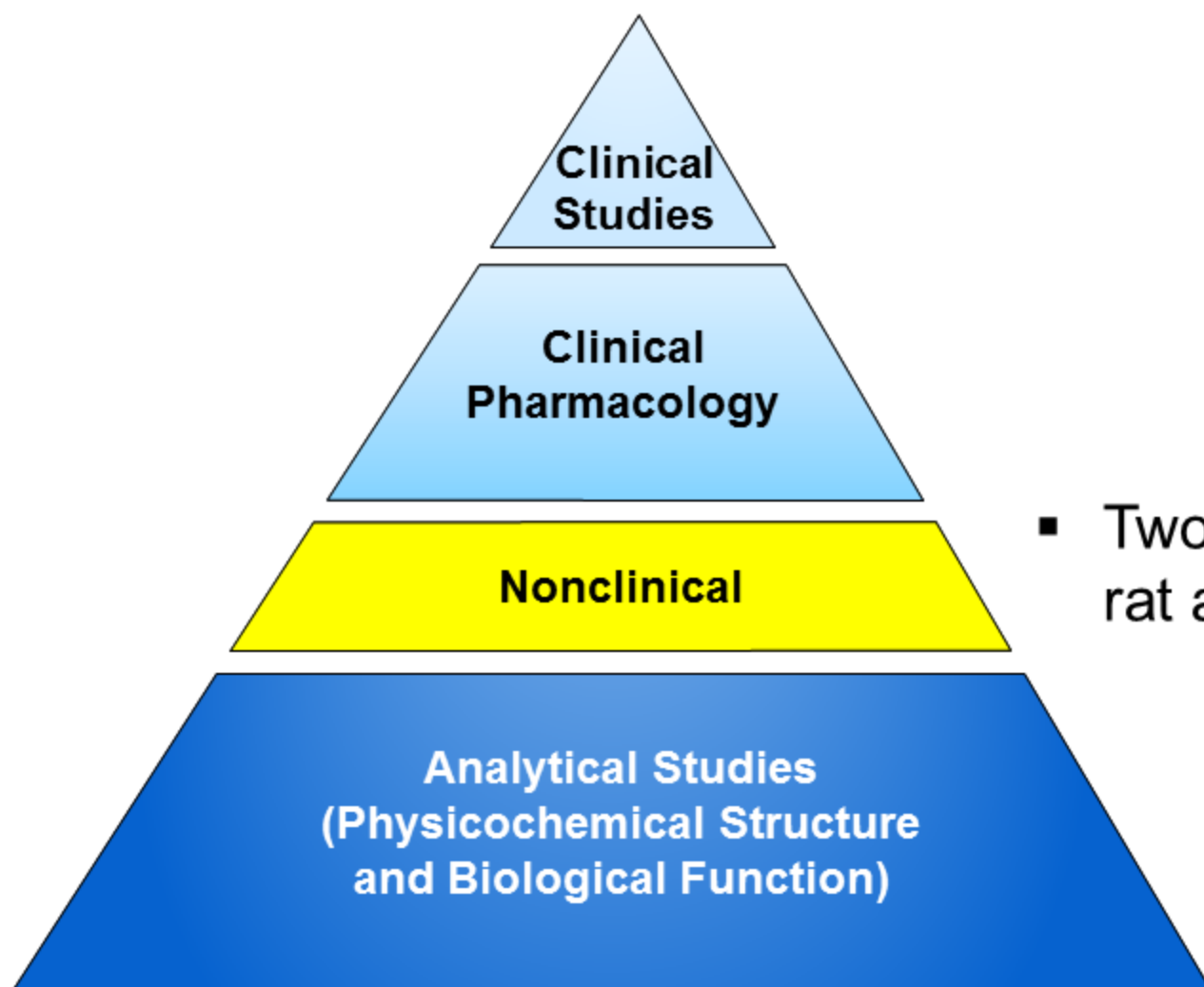


- Structure and function of Epoetin Hospira demonstrated to be highly similar to Epogen/Procrit in analytical studies
- Epoetin Hospira biosimilarity to reference product evaluated further through clinical studies

Nonclinical, Clinical Pharmacology and Clinical Biosimilarity Assessment

Nancy Martin, MD, PharmD, FCP

Nonclinical Studies to Support Biosimilarity



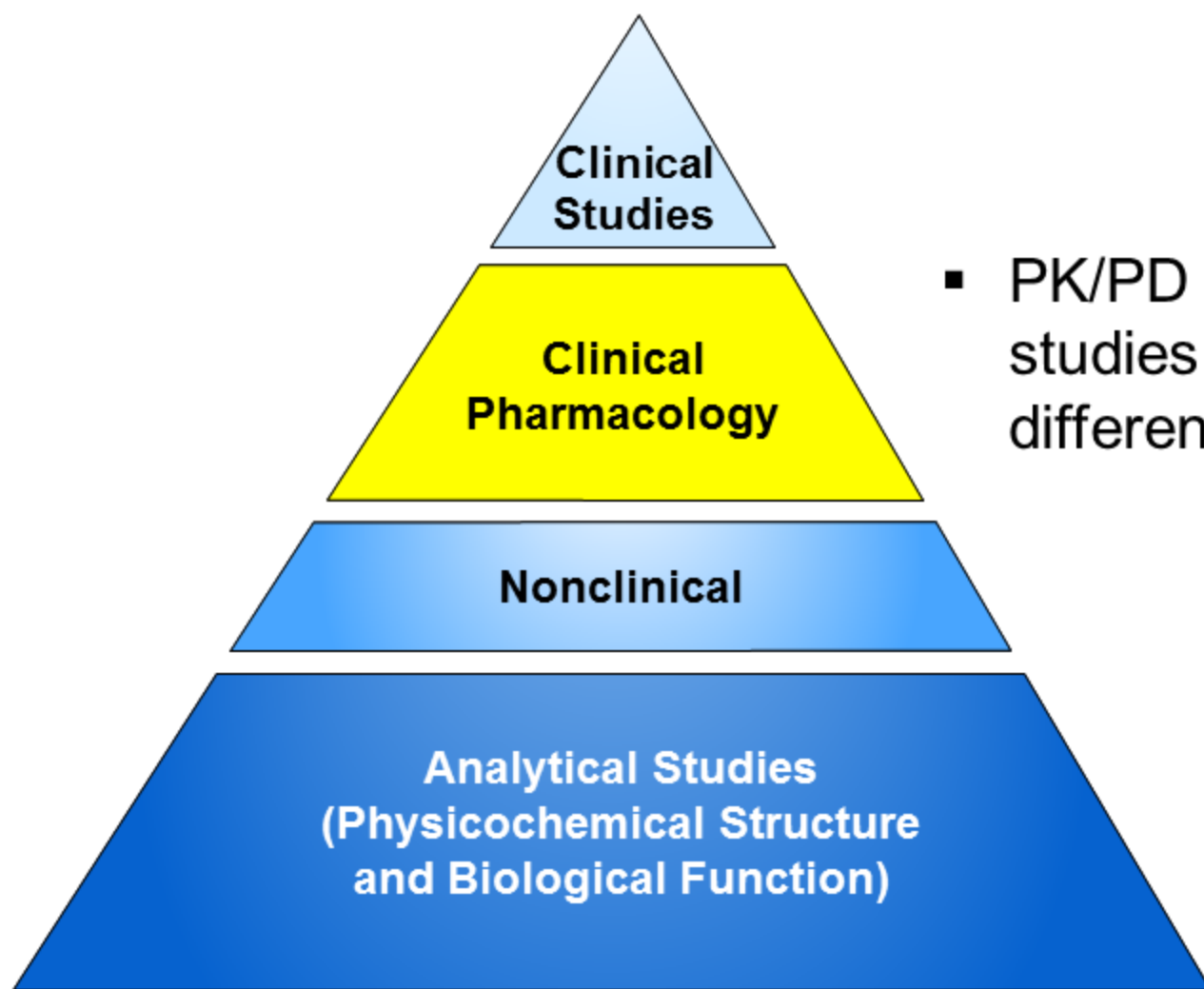
- Two 13-week toxicology studies in rat and dog support biosimilarity

Nonclinical Data in Support of Similarity

	Rat 13-week SC	Dog 13-week IV
Toxicology	<ul style="list-style-type: none"> Similar gross and microscopic pathology 	<ul style="list-style-type: none"> Similar gross and microscopic pathology
Immunogenicity	<ul style="list-style-type: none"> Higher immunogenicity in reference product likely due to HSA excipient 	<ul style="list-style-type: none"> Consistent, low incidence of immunogenicity
TK/PK	<ul style="list-style-type: none"> TK/PK confounded by differential immunogenicity 	<ul style="list-style-type: none"> Consistent TK/PK
PD	<ul style="list-style-type: none"> PD confounded by differential immunogenicity 	<ul style="list-style-type: none"> Consistent PD

- Nonclinical results in rat SC study did not translate to humans as confirmed with clinical PK/PD similarity and comparative clinical studies

Pharmacology Studies to Establish PK/PD Equivalence and Support Biosimilarity



- PK/PD studies most discerning clinical studies to detect *in vivo* performance differences, should they exist

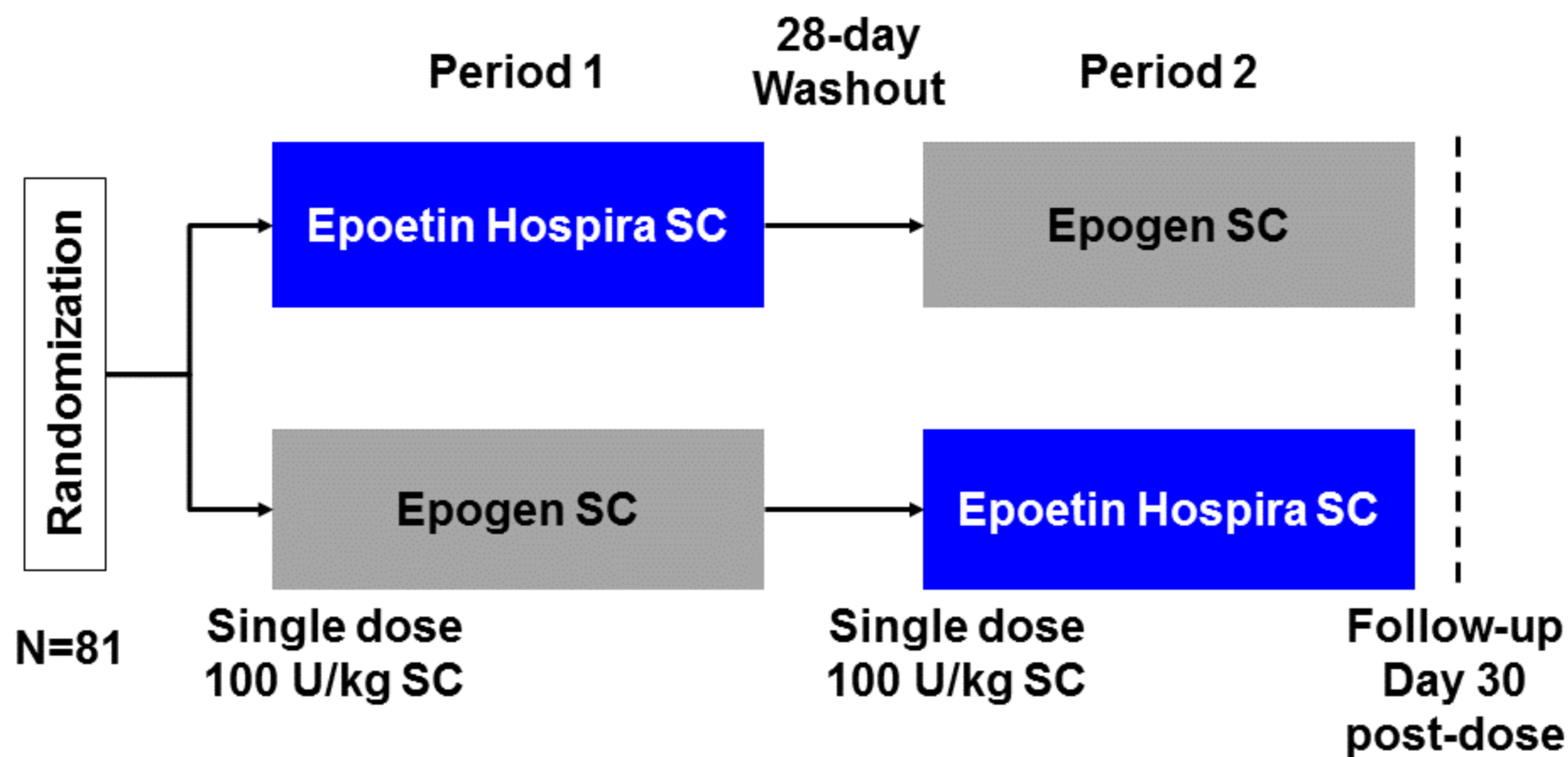
Two Studies Conducted to Demonstrate PK/PD Equivalence of SC Dosing

Study	Design	Population	Dosing	Subjects
Single dose PK/PD (EPOE 12-02)	Crossover	Healthy male subjects	Single 100 U/kg dose (SC)	N=81
Multiple dose PK/PD (EPOE 14-01)	Parallel	Healthy male subjects	Multiple 100 U/kg doses (SC) TIW x 4wks	N=129

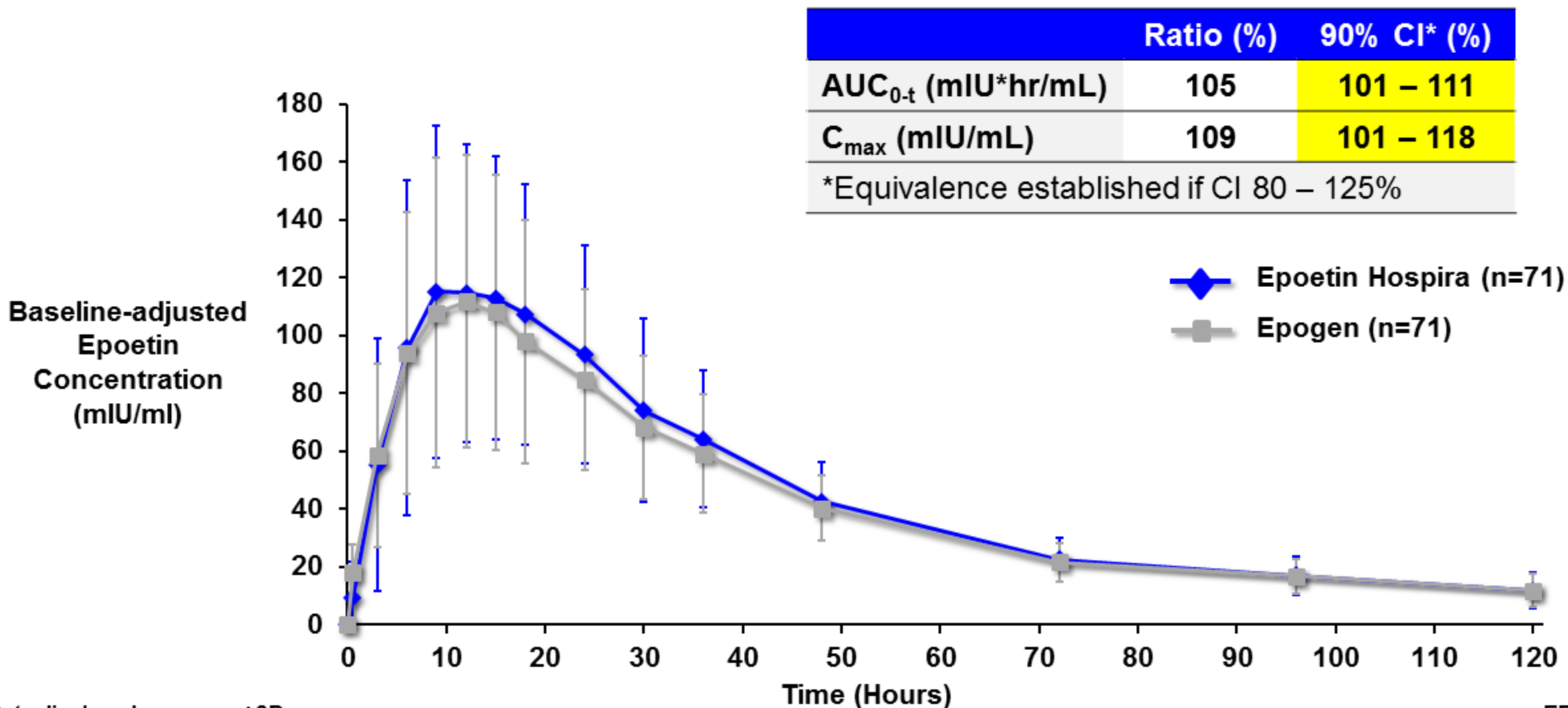
Epoetin Hospira Single Dose PK/PD Study

EPOE 12-02

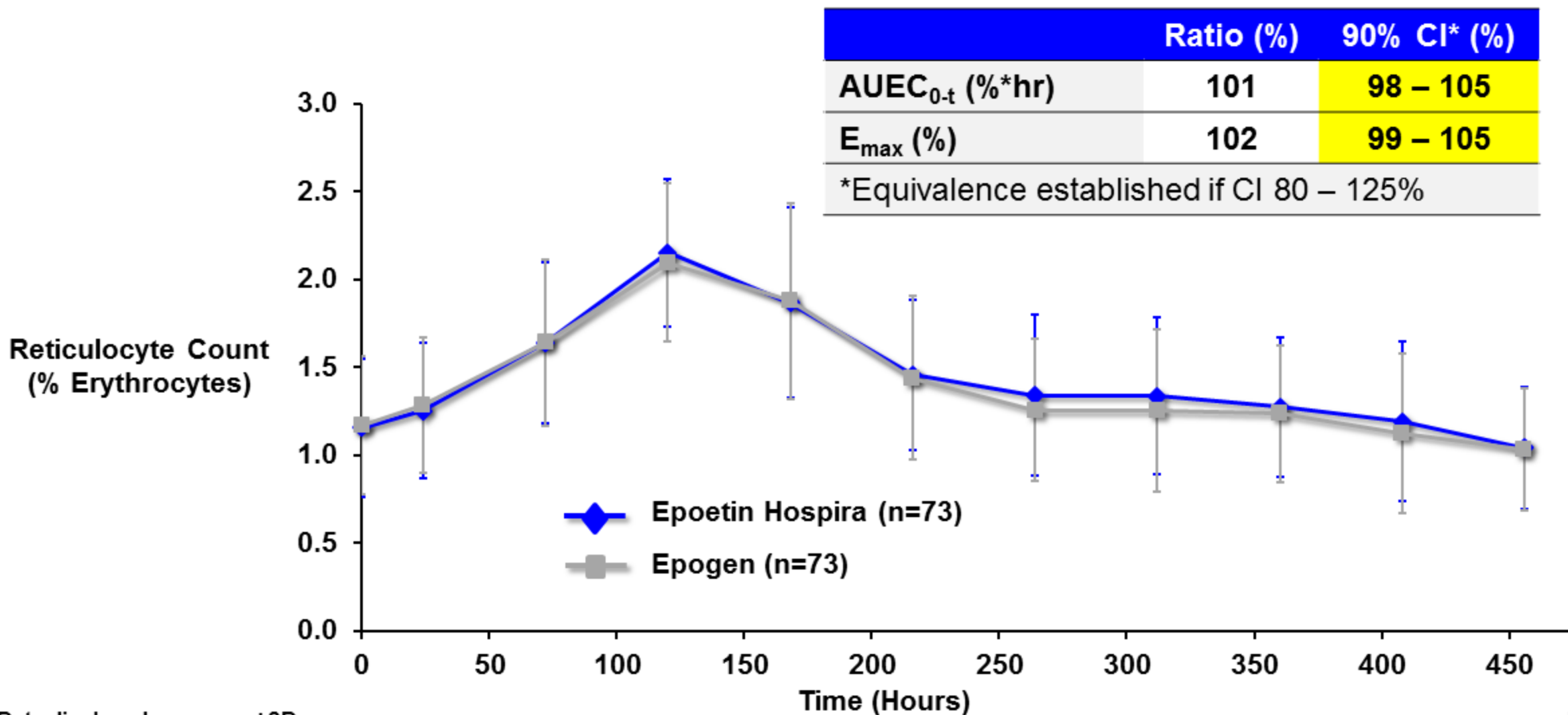
Single Dose PK/PD Study Used Randomized Crossover Design



Single Dose PK Equivalence Established Between Epoetin Hospira and Epogen



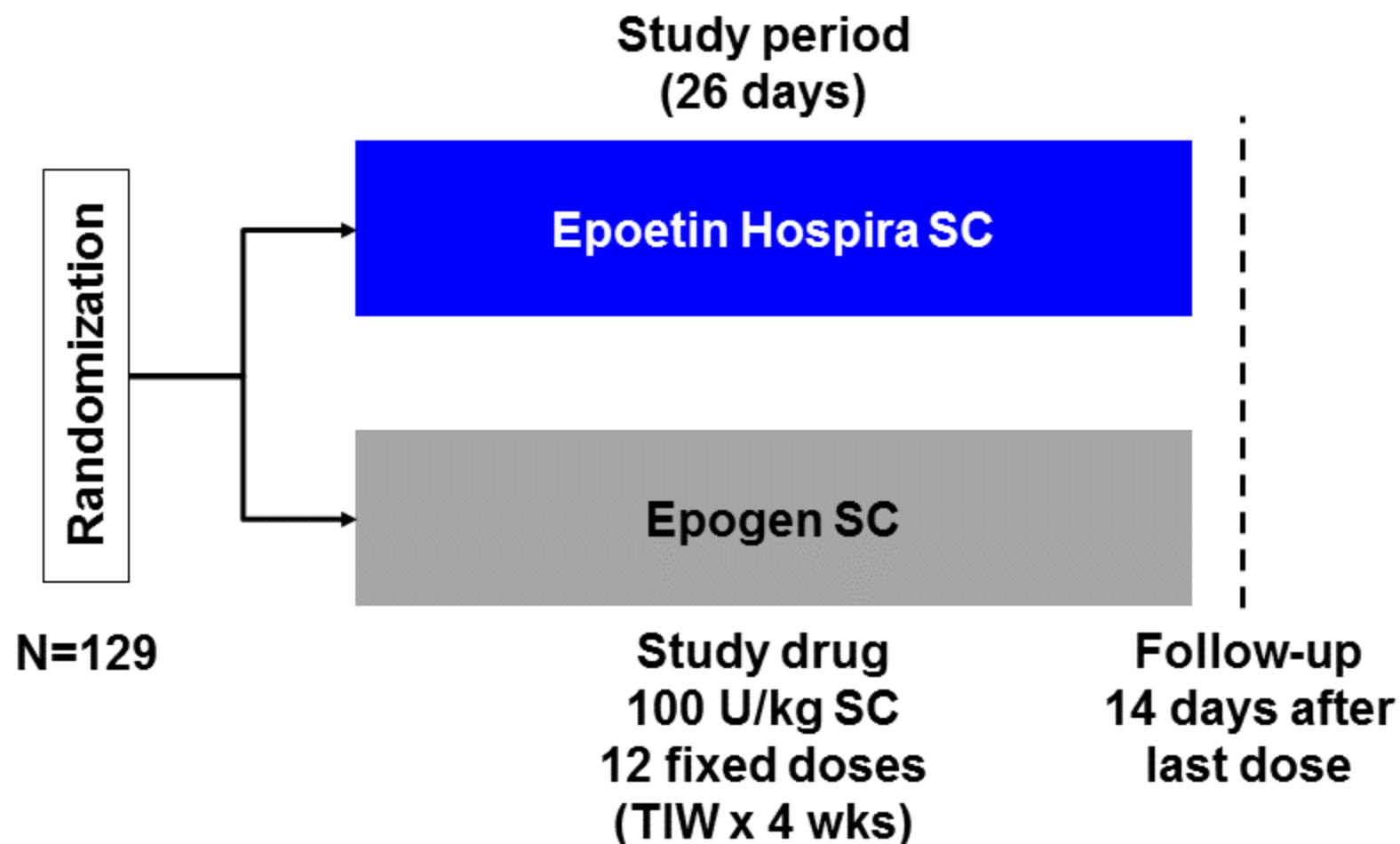
Single Dose PD Equivalence Established Between Epoetin Hospira and Epogen



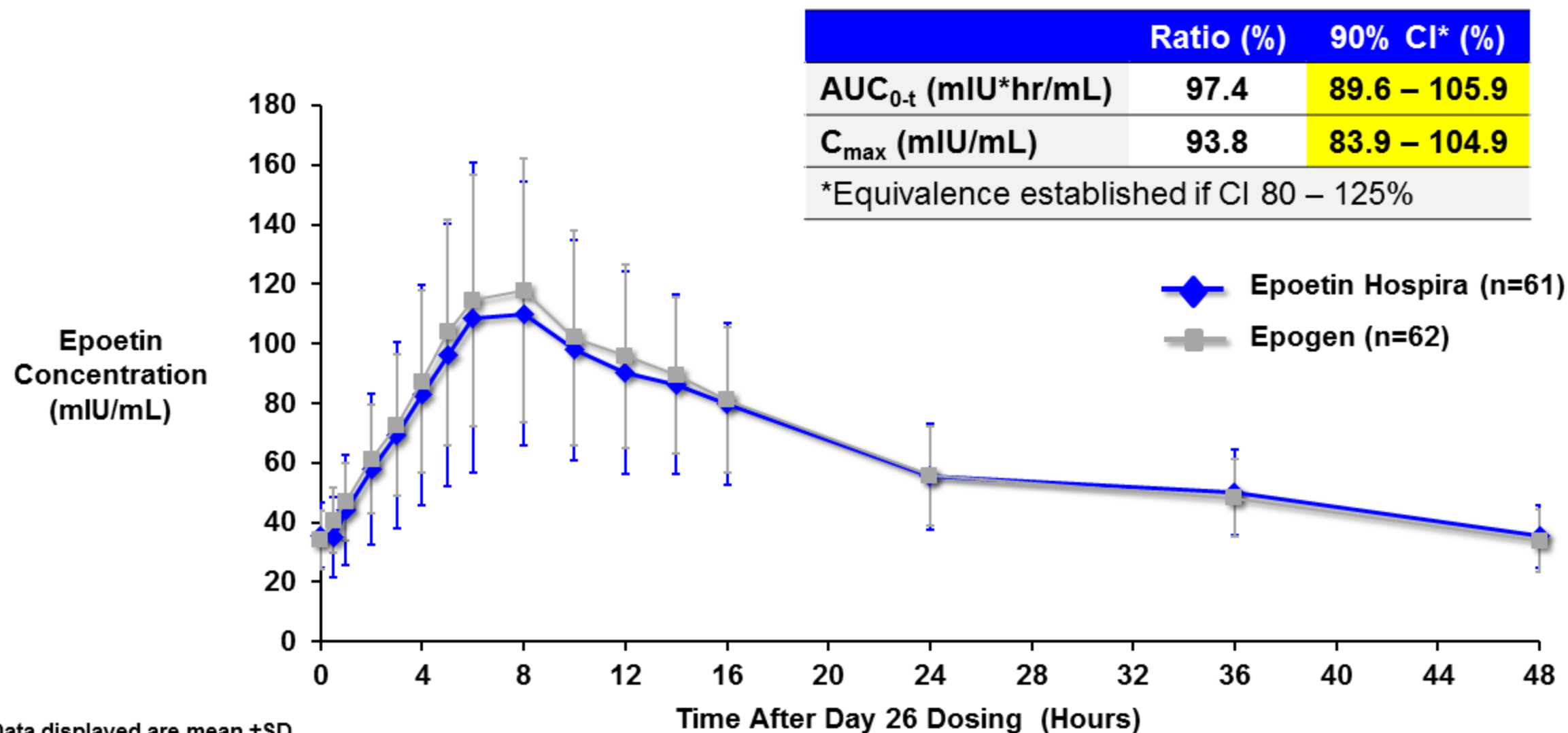
Epoetin Hospira Multiple Dose PK/PD Study

EPOE 14-01

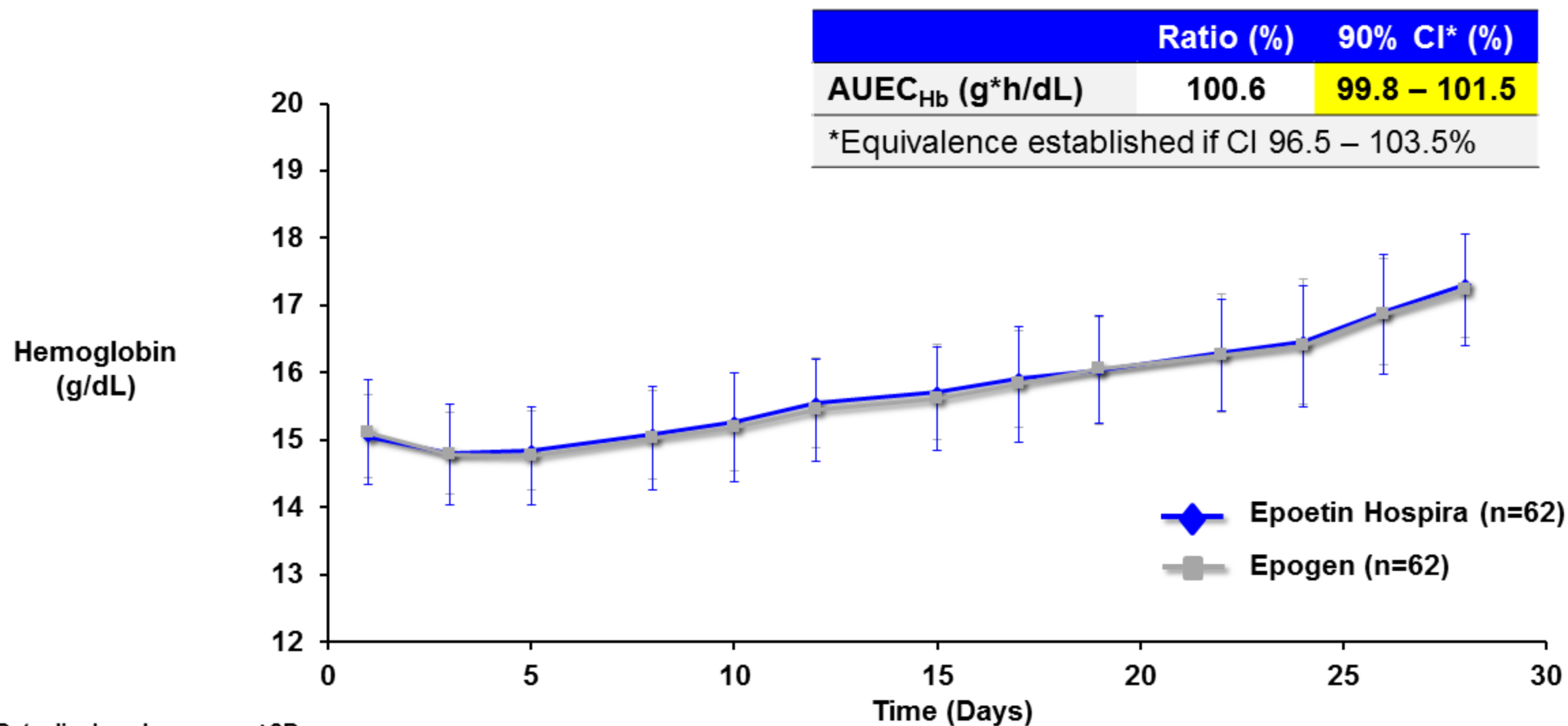
Multiple Dose PK/PD Study Used Randomized Parallel Design



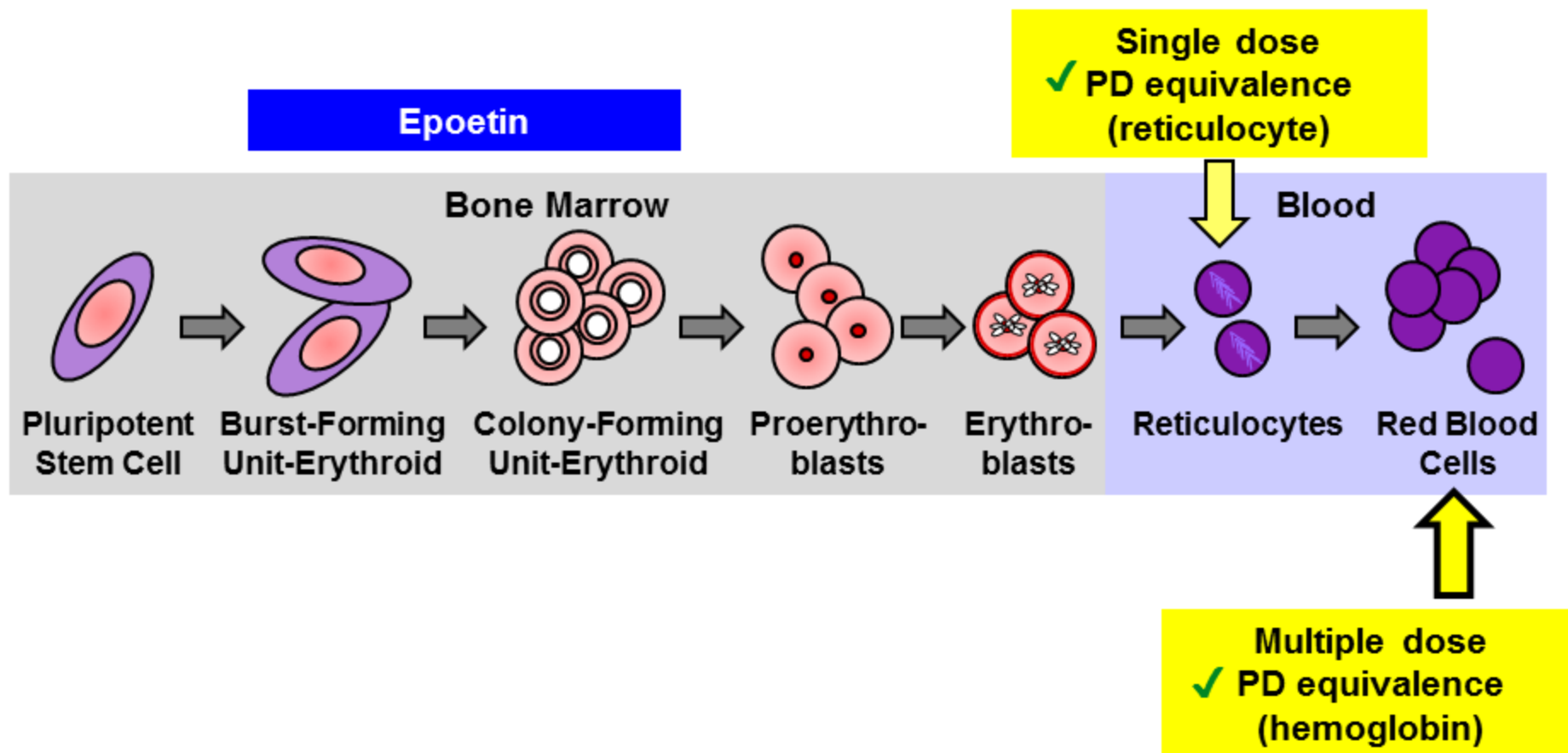
Multiple Dose PK Equivalence Established Between Epoetin Hospira and Epogen



Multiple Dose PD Equivalence Established Between Epoetin Hospira and Epogen

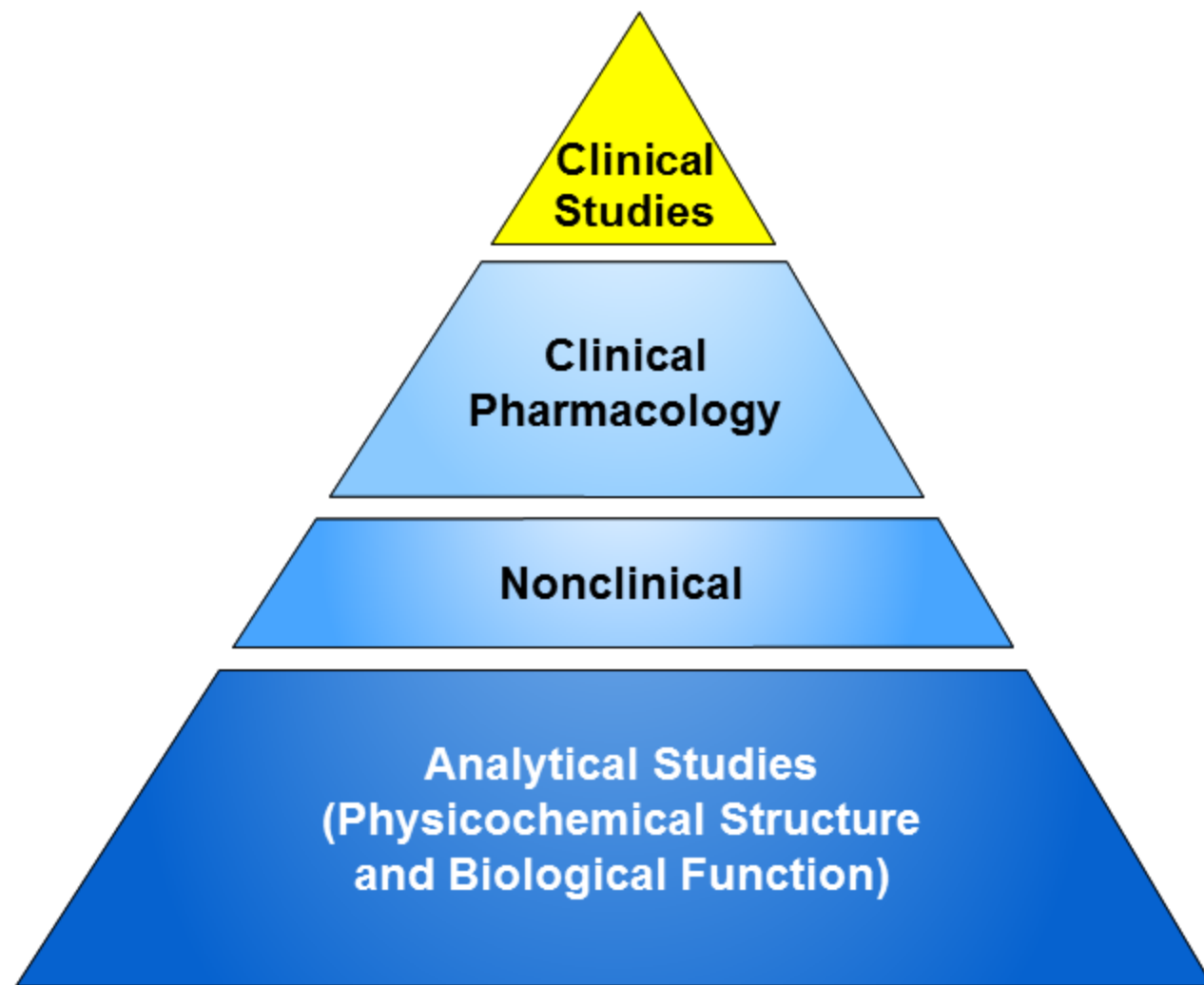


Mechanism of Epoetin Conserved Across All Conditions of Use



Clinical Efficacy

Clinical Studies to Establish Similar Efficacy and Safety



Two, Randomized, Controlled Trials Demonstrate Equivalence to Epogen

Study	Population	Dosing	Patients	PI	US Sites
Comparative SC Efficacy and Safety (EPOE 10-13)	Patients with CKD on dialysis	SC 1-3 doses/week	N=320	52	68
Comparative IV Efficacy and Safety (EPOE 10-01)	Patients with CKD on dialysis	IV 1-3 doses/week	N=612	78	95

- Option to enroll in long-term, open-label Epoetin Hospira safety study
- SC and IV administration evaluated in comparative clinical studies

Eligibility Criteria Align with Epoetin Guidelines, Study Precedent and Label

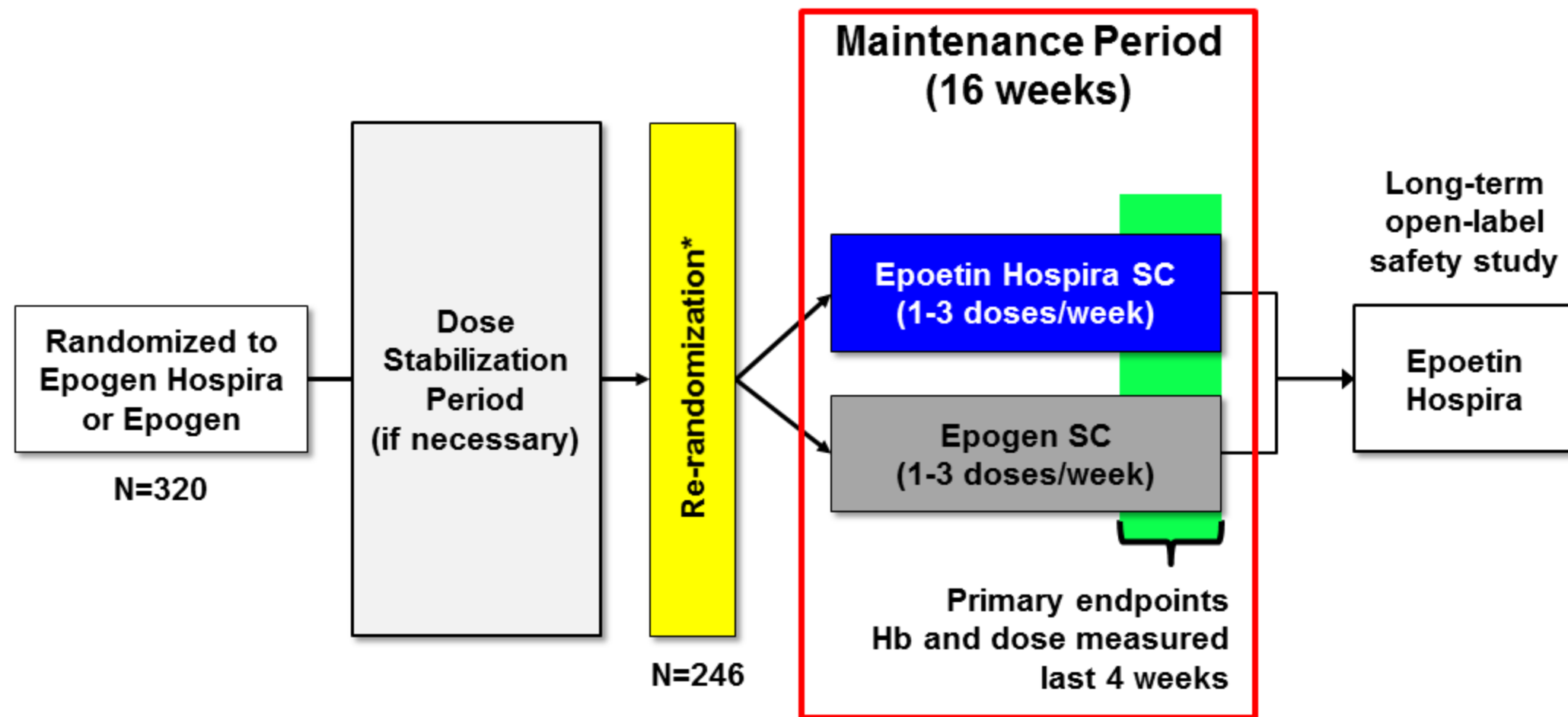
Key Inclusion

- Patients with CKD and anemia
- ≥ 12 weeks stable dialysis
- Adequate iron stores (plasma ferritin >100 mcg/L and TSAT $>20\%$)
- Stable Epogen treatment (Hb and dose)

Key Exclusion

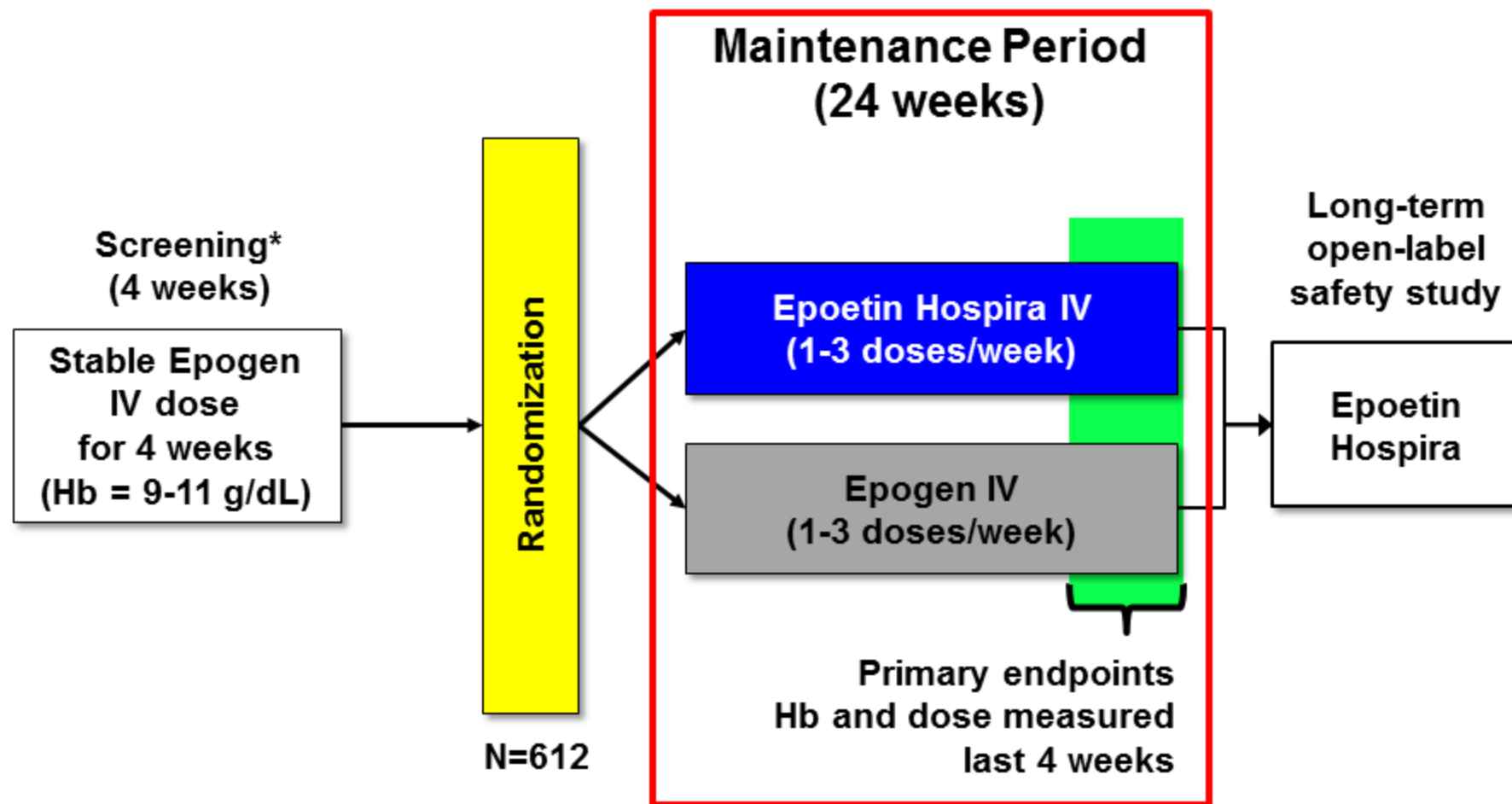
- CV SAE ≤ 3 months
- Folic acid or B12 deficiency
- History of disorders that affect RBC
 - Anti-rhEPO antibodies

Comparative SC Efficacy and Safety Study in Patients with CKD on Maintenance Therapy



*Patients were a) stable SC for ≥ 4 weeks at screening, b) stabilized on Epoetin Hospira SC over 12-18 weeks, or c) stabilized on Epogen SC over 12-18 weeks.

Comparative IV Efficacy and Safety Study in Patients with CKD on Maintenance Therapy



* IV Study had no stabilization period

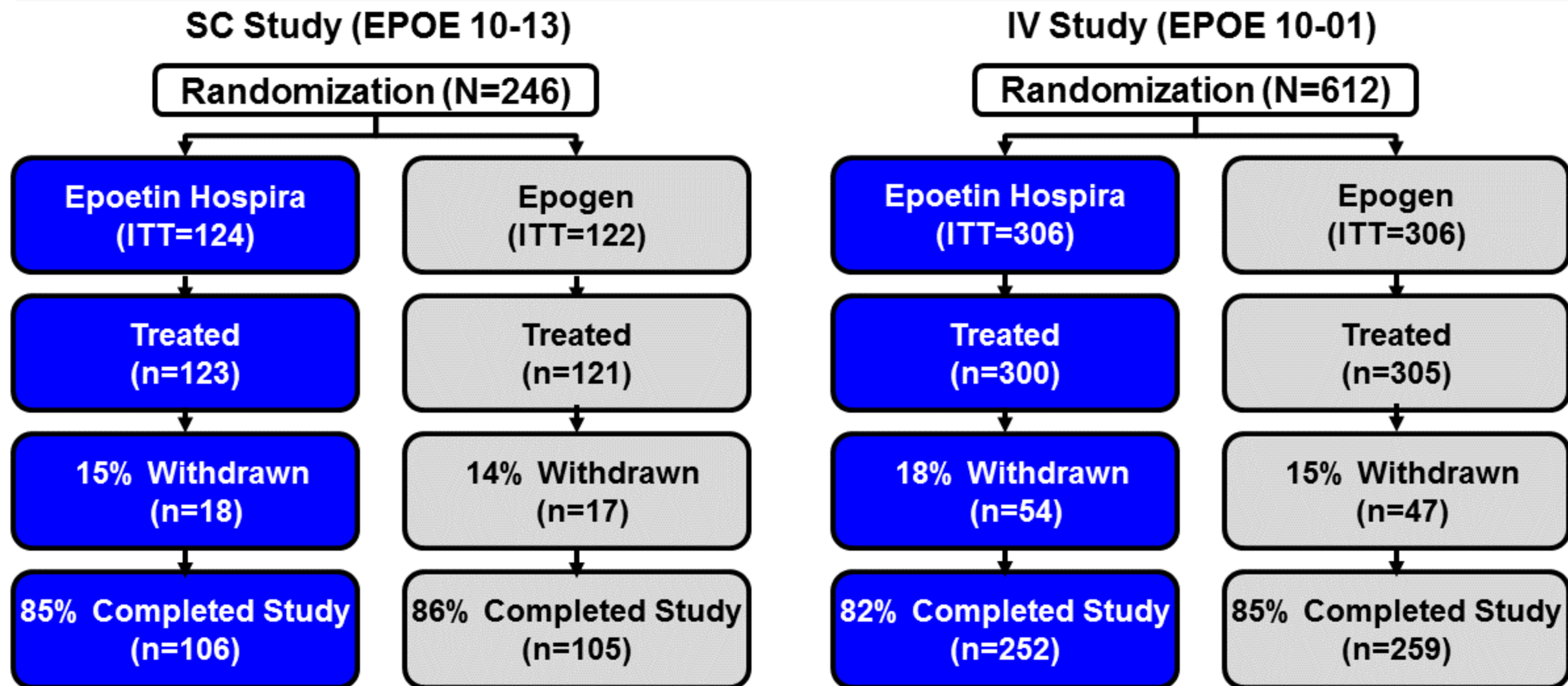
Co-Primary Endpoints for SC and IV Efficacy and Safety Studies

- Mean weekly hemoglobin levels
 - Hemoglobin used to titrate epoetin to clinical effect
- Mean weekly study drug dose

Equivalence Margins

- Similar efficacy if CIs entirely within pre-specified equivalence margins
- Equivalence margins based on published Hb data, treatment target, and epoetin dosing data in patients with CKD on hemodialysis
 - Hb ± 0.5 g/dL
 - Dose ± 45 U/kg/week
- ANCOVA model used

Disposition Similar Between Treatment Groups



Demographics Consistent Between Treatment Groups in Patients with CKD

Category	SC Study (EPOE 10-13)		IV Study (EPOE 10-01)	
	Epoetin Hospira (n=124)	Epogen (n=122)	Epoetin Hospira (n=306)	Epogen (n=306)
Mean age (SD)	57 (11.9)	57 (13.5)	55 (13.1)	57 (11.4)
% Female	48%	54%	48%	43%
Race				
White	56%	48%	46%	49%
Black	40%	48%	49%	42%
Other*	4%	3%	5%	9%
Weight (kg) (SD)	85 (22.9)	87 (25.3)	87 (23.6)	87 (22.5)

- Study demographics representative of US patients with CKD on hemodialysis

Disease Characteristics Consistent Between Treatment Groups

Category	SC Study (EPOE 10-13)		IV Study (EPOE 10-01)	
	Epoetin Hospira (n=124)	Epogen (n=122)	Epoetin Hospira (n=306)	Epogen (n=306)
Baseline Hb (SD)	10.4 (0.8)	10.3 (0.8)	10.4 (0.8)	10.4 (0.7)
Baseline dose U/kg/week (SD)	93.6 (111.5)	86.3 (83.2)	106.0 (97.5)	107.6 (103.9)
Baseline % TSAT (SD)	36 (13.4)	34 (14.5)	34 (11.7)	33 (10.9)
Baseline ferritin ng/mL (SD)	982 (413.2)	929 (398.8)	925 (443.2)	937 (417.9)
CKD primary cause				
Diabetes	45%	34%	47%	49%
Hypertension	35%	48%	34%	28%
Nephropathies	10%	13%	12%	14%
Other*	10%	6%	6%	8%

*Other inclusive of unknown

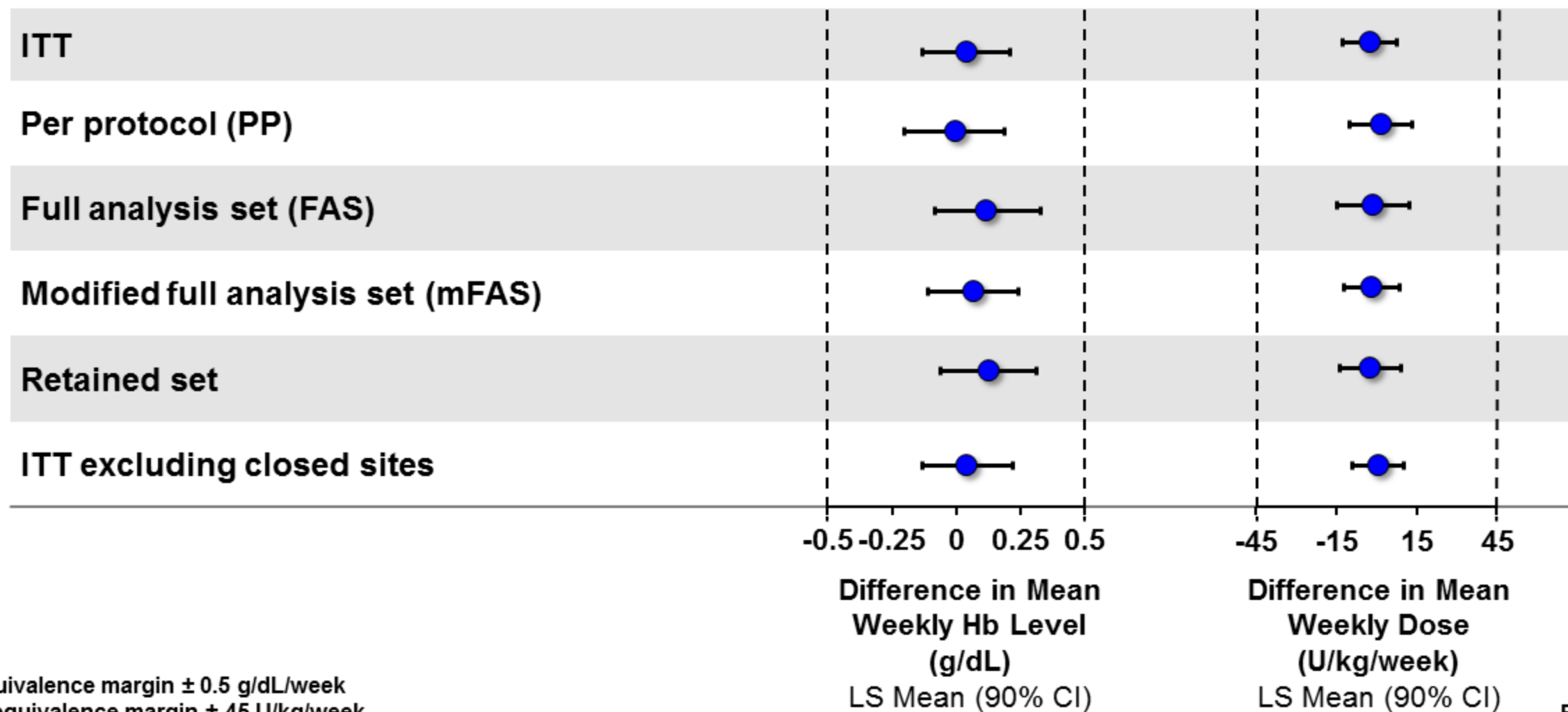
SC: Co-Primary Endpoints Within Pre-specified Margins, Supporting Similarity

Efficacy and Safety SC Study Co-primary Endpoints	Epoetin Hospira (n=124)	Epogen (n=122)
LS mean weekly Hb (g/dL) during last 4 weeks maintenance (SE)	10.2 (0.07)	10.1 (0.07)
Difference LS means	0.04	
(90% CI)	(-0.13, 0.21) equivalence margin ± 0.5 g/dL/week	
LS mean weekly dose (U/kg/week) during last 4 weeks maintenance (SE)	79.6 (4.4)	81.9 (4.4)
Difference LS means	-2.34	
(90% CI)	(-12.54, 7.85) equivalence margin ± 45 U/kg/week	

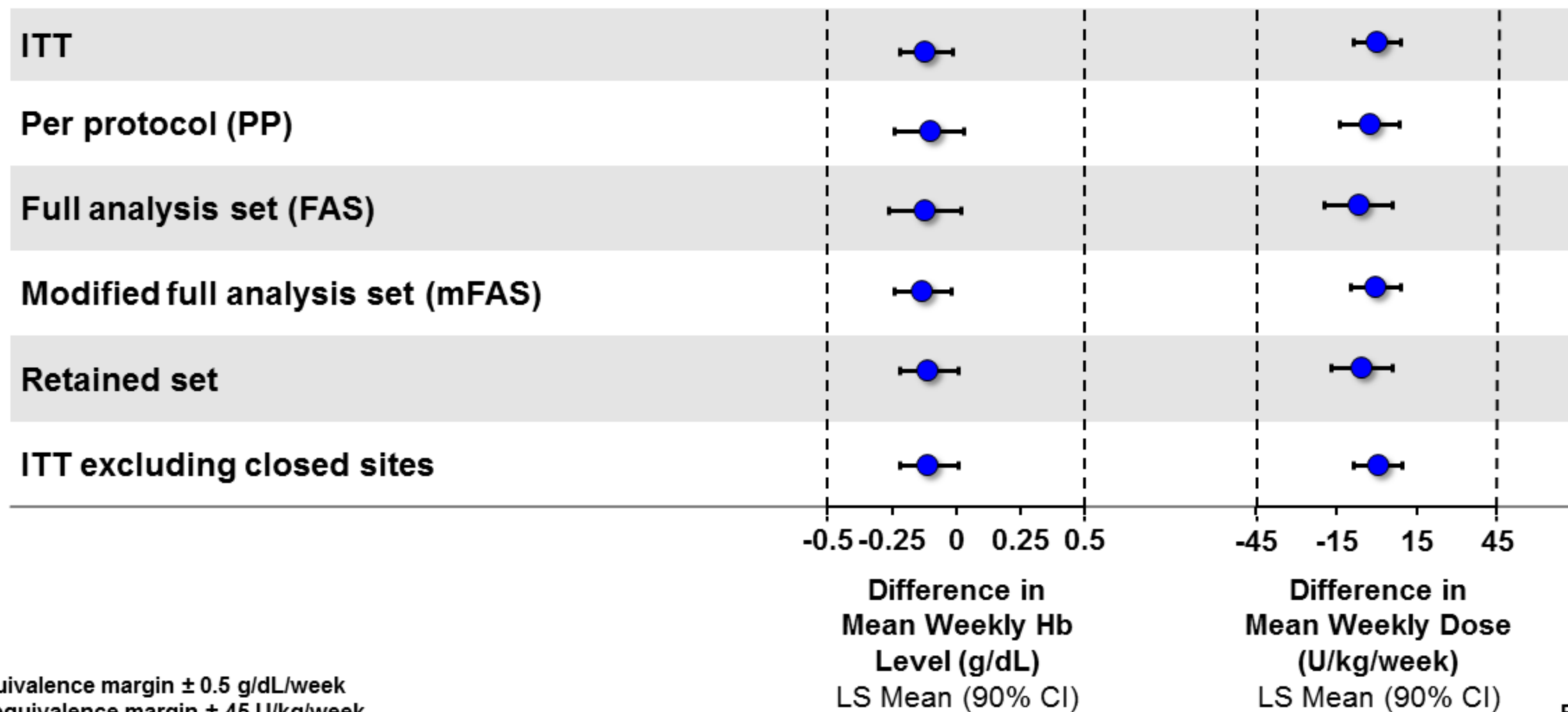
IV: Co-Primary Endpoints Within Pre-specified Margins, Supporting Similarity

Efficacy and Safety IV Study Co-primary Endpoints	Epoetin Hospira (n=306)	Epogen (n=306)
LS mean weekly Hb (g/dL) during last 4 weeks maintenance (SE)	10.2 (0.05)	10.3 (0.05)
Difference LS means	-0.12	
(90% CI)	(-0.22, -0.01) equivalence margin ± 0.5 g/dL/week	
LS mean weekly dose (U/kg/week) during last 4 weeks maintenance (SE)	90.2 (3.9)	89.8 (3.9)
Difference LS means	0.37	
(90% CI)	(-8.67, 9.40) equivalence margin ± 45 U/kg/week	

SC: Sensitivity Analyses Support ITT Conclusions



IV: Sensitivity Analyses Support ITT Conclusions



Key Secondary Endpoints Consistent with Co-Primary Results

Key Secondary Endpoints From SC Study (EPOE 10-13)	Epoetin Hospira (n=124)	Epogen (n=122)
Patients with weekly mean Hb between 9-11 g/dL at Week 16	80%	74%
Patients receiving blood transfusions at any time	4%	4%
Key Secondary Endpoints From IV Study (EPOE 10-01)	Epoetin Hospira (n=306)	Epogen (n=306)
Patients with weekly mean Hb between 9-11 g/dL at Week 24	73%	71%
Patients receiving blood transfusions at any time	6%	6%

Clinical Safety

SC and IV: Primary Safety Overview Includes Pooled Data from 2 Randomized Controlled Studies

Study	Enrollment	Dosing
Comparative SC Efficacy and Safety (EPOE 10-13)	CKD patients on dialysis	SC 1-3 doses/week
Comparative IV Efficacy and Safety (EPOE 10-01)	CKD patients on dialysis	IV 1-3 doses/week

Adverse Events Consistent Between Groups

Parameter	Epoetin Hospira (N=423)	Epogen (N=426)
	%	%
Patients reporting ≥ 1 AE	76	75
Patients reporting ≥ 1 severe AE	15	16
Patients reporting ≥ 1 related AE	3	4
Patients reporting ≥ 1 SAE	24	27
Patients discontinuing study due to AE	3	4
Deaths	2	2

Reported Common AEs $\geq 5\%$ in Either Treatment Group

System Organ Class	Preferred Term	Epoetin Hospira (N=423)	Epogen (N=426)
		%	%
Gastrointestinal disorders	Diarrhea	6.1	7.7
	Nausea	9.5	7.7
	Vomiting	7.6	4.9
Injury, poisoning, and procedural complication	Arteriovenous fistula site complication	7.6	7.0
	Fall	5.2	3.8
Musculoskeletal and connective tissue disorder	Muscle spasm	7.3	6.6
	Pain in extremity	4.0	5.2
Nervous system disorder	Dizziness	5.4	5.9
	Headache	6.9	4.5
Respiratory, thoracic and mediastinal disorders	Cough	5.0	5.9
	Dyspnea	5.9	6.1
Vascular disease	Hypertension	5.7	4.5
	Hypotension	3.5	6.8

Consistent SAE Rates $\geq 1\%$

Preferred Term	Epoetin Hospira (N=423)	Epogen (N=426)
	%	%
Patients reporting ≥ 1 SAE	24	27
Pneumonia	1.7	2.3
Cardiac failure congestive	1.2	1.2
Osteomyelitis	1.2	0.2
Non-cardiac chest pain	0.9	1.9
Dyspnea	0.7	1.9
Fluid overload	0.2	1.6
Hyperkalemia	0.9	1.4
Cellulitis	0.7	1.4

Event of Interest – Thromboembolism

Parameter	Epoetin Hospira (N=423)		Epogen (N=426)	
	n	%	n	%
Number of thromboembolic events	39		36	
Patients with ≥ 1 thromboembolic event	33	7.8	26	6.1
Patients with serious thromboembolic events	8	1.9	14	3.3
Patients with severe thromboembolic events	5	1.2	10	2.3
Patients with treatment-related thromboembolic events	0	-	1	0.2

Event of Interest – Hypertension

Parameter	Epoetin Hospira (N=423)		Epogen (N=426)	
	n	%	n	%
Number of hypertension events	33		32	
Patients with ≥ 1 hypertension event	28	6.6	21	4.9
Patients with serious hypertension events	3	0.7	4	0.9
Patients with severe hypertension events	1	0.2	0	-
Patients with treatment-related hypertension events	0	-	0	-

Other Events of Interest

Events of Interest	Epoetin Hospira (N=423)	Epogen (N=426)
	%	%
Potential allergic reaction	2.4	1.4
Myocardial infarction	0.9	0.7
Cerebrovascular	0.9	1.4
Seizure	0.2	0.2
Pure red cell aplasia	0	0

Immunogenicity Assessments Conducted Throughout Studies

- Validated assays
 - Anti-epoetin drug antibody (ADA) by RIP
 - Neutralizing antibodies (NAb) by cellular assay
- Serum samples collected throughout studies

Similar Immunogenicity Between Epoetin Hospira and Epogen

	Epoetin Hospira (N=423)	Epogen (N=426)
Baseline	n=378	n=370
Positive ADA, n (%)	3 (0.8%)	4 (1.1%)
At any time during treatment period	n=393	n=397
Positive ADA, n (%)	4 (1.0%)	4 (1.0%)

- No neutralizing antibodies detected in any patient
- No reported events of pure red cell aplasia in clinical program

Clinical Program Supports Demonstration of Biosimilarity

- Established PK and PD equivalence
- Similar clinical efficacy
- Consistent safety and immunogenicity
- No clinically meaningful differences

Conclusion Supporting Biosimilarity and Extrapolation Across All Indications

Sumant Ramachandra, MD, PhD

Senior VP, Research and Development Head
Pfizer Essential Health

Analytical Studies Demonstrate Epoetin Hospira Highly Similar to Epogen/Procrit

Analytical	Supports Biosimilarity
Same dose strengths	✓
Primary structure – identical amino acid sequence	✓
Higher order structure – including N- and O-glycans	✓
Related substances and impurities	✓
Functional activity	✓
Equivalent <i>in vivo</i> biopotency	✓
Equivalent <i>in vitro</i> specific activity	✓

Development Program Demonstrated No Clinically Meaningful Differences

Clinical Pharmacology		Supports Biosimilarity
PK and PD equivalence in single dose study		✓
PK and PD equivalence in multiple dose study		✓
Comparative Efficacy and Safety		
Efficacy equivalence – SC administration		✓
Efficacy equivalence – IV administration		✓
Consistent safety profile		✓
Consistent immunogenicity profile		✓

Extrapolation Supported by Biosimilarity and Knowledge of Reference Product



Justification for Extrapolation Across All Indications

MoA in each condition of use

Epoetin action on erythropoiesis consistent across all indications

PK and biodistribution

Well-characterized PK/PD relationship across various populations

Immunogenicity

Evaluated in all approved routes of administration, well-characterized profile across populations

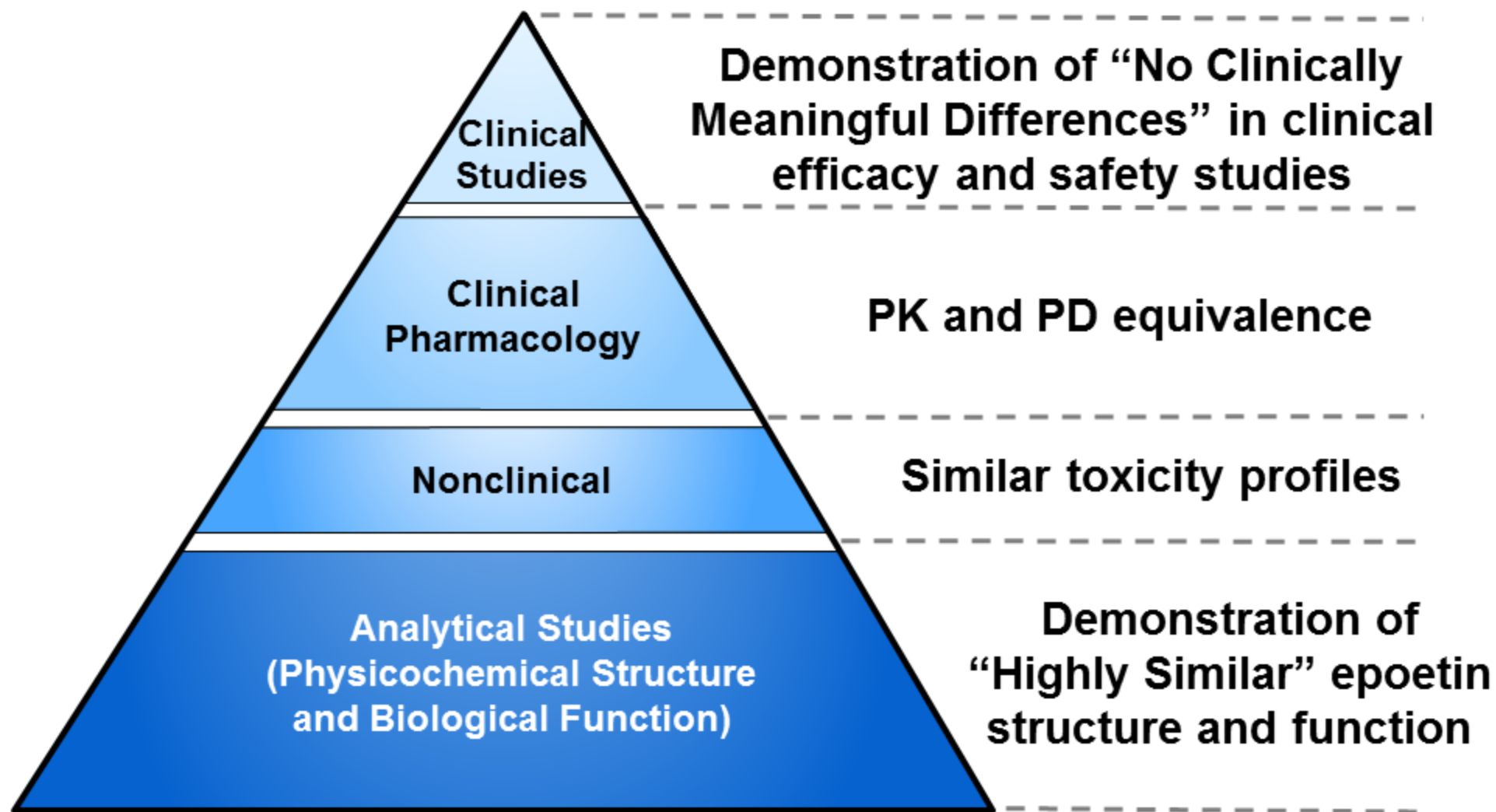
Expected toxicities

Well-characterized toxicities for reference product

Additional considerations

Well-characterized SC and IV routes of administration

Totality of Data Demonstrates Epoetin Hospira is Biosimilar to Epogen/Procrit Across All Indications



Epoetin Hospira Biosimilar Application to Epogen[®]/Procrit[®] (epoetin alfa)

May 25, 2017

FDA Oncologic Drugs Advisory Committee
Hospira Inc., a Pfizer company

Back-up Slides

EU Retacrit Oncology Experience in >4700 Study Patients

Study	N	Hb Response Rate	VTE
ORHEO (France)	2333	81.6% 3 mth 86.5% 6 mth	2.4% 3 mth 1.5% 6 mth
SYNERGY (France)	2167	69-81%	2%
ORHEO (Germany)	291	84.8%	2.4%
04-46 Clinical Study	216	81.5%	4.2%

EU Retacrit has been marketed since 2007 with > 363,000 patient-years exposure

Abbreviation: CIA = Chemotherapy induced Anemia
 Michallet et al 2014. NCT02140736.
 Scotte et al 2015. NCT02158169.
 Losem et al 2017. NCT01626547.
 Tzekova et al 2009. EudraCT2005-004292-38.

EU Experience No Difference with Immunogenicity

Biosimilars

Dovepress

open access to scientific and medical research

 Open Access Full Text Article

REVIEW

Multidisciplinary approach to evaluating immunogenicity of biosimilars: lessons learnt and open questions based on 10 years' experience of the European Union regulatory pathway

This article was published in the following Dove Press journal:

Biosimilars

25 June 2014

[Number of times this article has been viewed](#)

Paul D Chamberlain

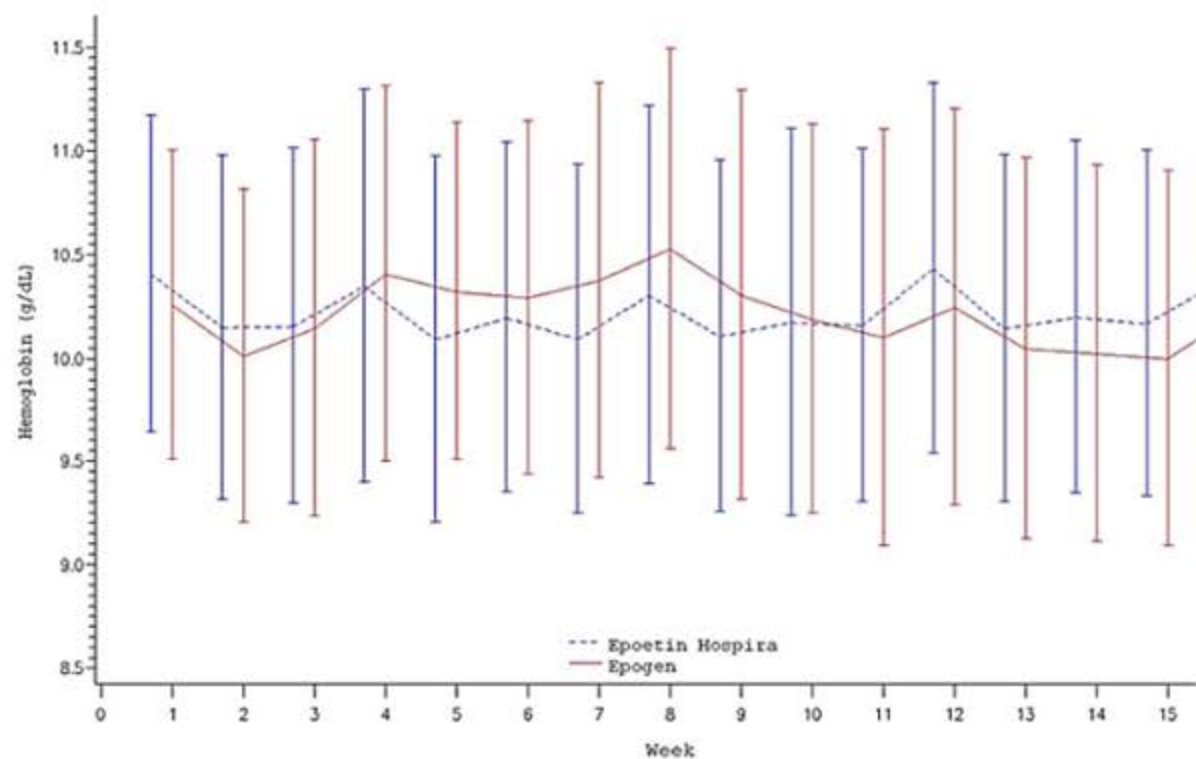
NDA Advisory Board, NDA Advisory
Services Ltd, Surrey, UK

Abstract: Clinical evaluation of comparative immunogenicity represents an important component of the European Union regulatory review process for candidate biosimilar products. The clinical evaluation is part of a multidisciplinary review that cross-refers to product quality attributes as well as preclinical and ongoing risk management considerations. Results from the monitoring of anti-drug antibody formation in relevant populations treated for an adequate period

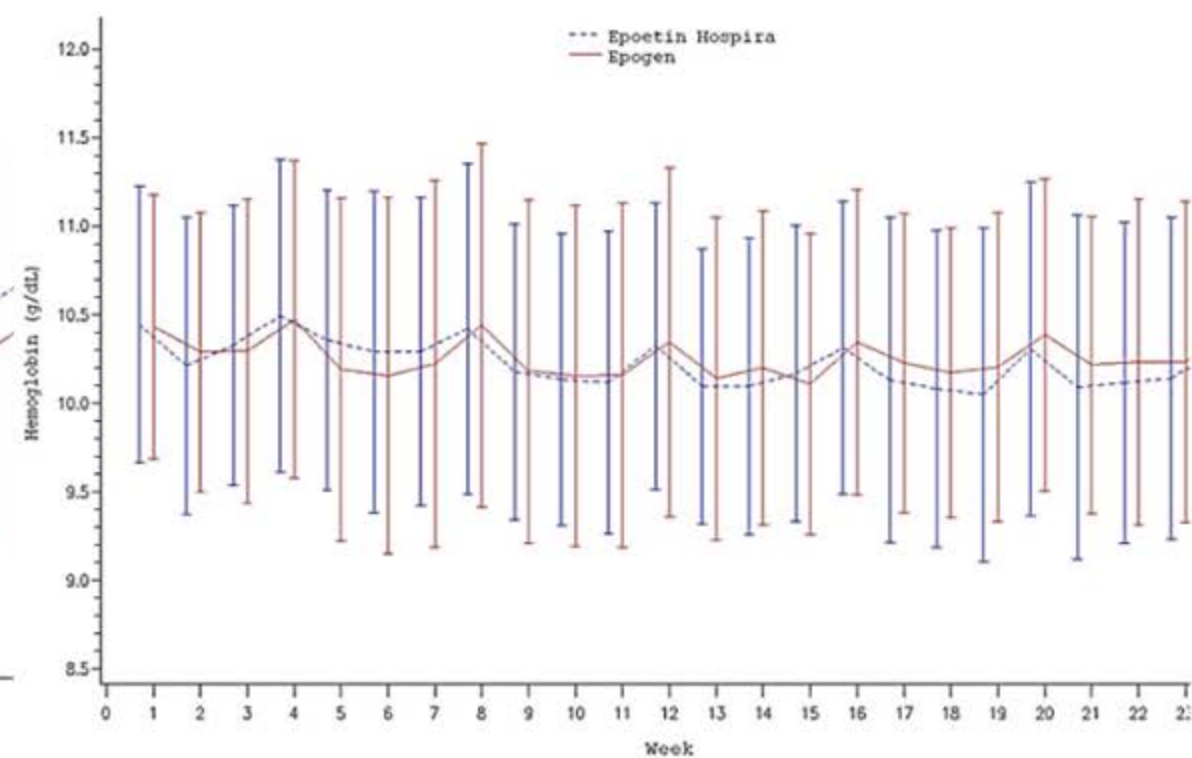
- No observed differences in clinically relevant immunogenicity between the approved biosimilar and originator products following authorization by EMA

EPO Figure 40. Mean Weekly Hemoglobin Level (g/dL) (\pm SD) during the Maintenance Period of the Subcutaneous Comparative Efficacy and Safety Study (Study 10-13) and Treatment Period of the Intravenous Comparative Efficacy and Safety Study (Study 10-01) (Intent-to-Treat Population)

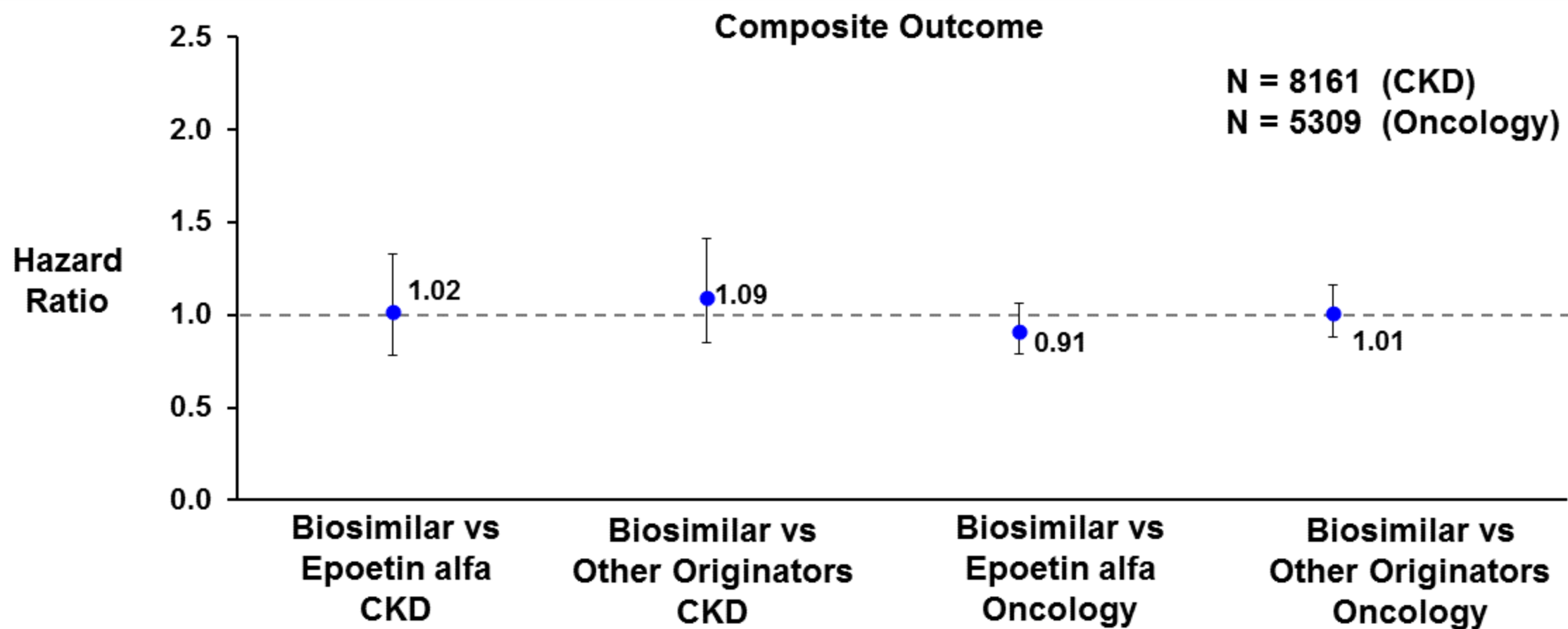
EPOE-10-13



EPOE-10-01



Similar Efficacy and Safety with Biosimilars Compared to Reference ESA Products: Population-based observational cohort study in Italy (13,470 cases)



Endpoint: Composite outcome (all-cause mortality, blood transfusion, MACE, blood dyscrasias)

Composite Outcome: several components combined into a single measure

Trotta et al BMJ Open 2017;7:e011637. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy

Subjects Excluded from Primary PK/PD Analysis

Pharmacodynamic Population (8 of 81 randomized)

- 6 subjects received treatment in Period 1 only
- 1 subject positive for anti-rhEPO antibody at pre-dose and throughout study conduct
- 1 subject received both treatments but dropped from study after 6 hour sample in Period 2

Pharmacokinetic Population (10 of 81 randomized)

- An additional 2 subjects were excluded due to insufficient data to calculate the primary PK parameters

Epoetin Hospira and EU Retacrit Analytically Comparable

Attribute	Comparability Confirmed
Primary Structure	✓
Higher-Order Structure	✓
N-Linked Glycan Profile (including levels of individual antennary structures and numbers of lactosamine repeats)	✓
Total Sialic Acids	✓
O-Linked Glycan Profile	✓
Isoform Distribution	✓
Product-Related Substances and Impurities (including deamidation, Asp isomerization, oxidation, disulfide scrambled species)	✓
High Molecular Weight Species	✓
T5 Trisulfide	Higher levels observed in EU Retacrit
<i>In Vitro</i> and <i>In Vivo</i> Specific Activities	✓

No Statistically Significant Difference in Timing of Subject Discontinuation Between Epoetin Hospira and Epogen Arms

