New Erythropoiesis Stimulating Agents

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University of California San Diego

Symposium on Pediatric Dialysis
Sunday March 12, 2017
5:35-6:00 PM

Objectives

- Briefly discuss Concerns Regarding Current Exogenous Erythropoietin Replacement Therapy
- Review The Roles Of Accelerators and Inhibitors In The Regulation of Erythropoiesis
- Explore New Erythropoiesis Stimulating Agents (ESA)
  - ANTI-INHIBITORS
    - Prolyl hydroxylase inhibitors
  - ACELERATORS
    - Fusion proteins
    - Erythropoietin-mimetics

Why go through the trouble of developing a new ESA?

Rank	Brand Name	Generic Name	Sales Q1 2014 ($000)	Change from Q4 2013	Companies	Disease	First approval date	Patent expiration date
22	Epogen	Epoetin alfa	503,493	-2.08%	Amgen	Anemia	Jun-1989	Mon-20XX
63	Procrit, Eprex	Epoetin alfa	241,535	-10.09%	Johnson & Johnson	Anemia	Dec-1990	Mon-20XX
94	Aranesp	Darbepoetin alfa	185,225	-9.22%	Amgen Inc.	Anemia	Jun-2001	Mon-20XX

https://en.wikipedia.org/wiki/List_of_largest_selling_pharmaceutical_products

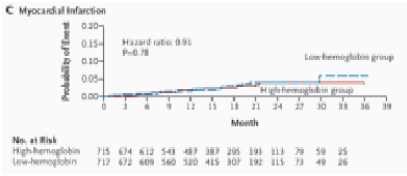
Concerns regarding exogenous erythropoietin: safety

- WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS, AND TUMOR PROGRESSION OR RECURRENCE.
- *Chronic Kidney Disease:*
  - In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
  - No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
  - Use the lowest EPOGEN® dose sufficient to reduce the need for red blood cell (RBC) transfusions.
- *Cancer:*
  - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
  - Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense EPOGEN® to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance.
  - To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
  - Use ESAs only for anemia from myelosuppressive chemotherapy.
  - ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
  - Discontinue following the completion of a chemotherapy course.
- *Perisurgery:*
  - Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended.

http://www.epogen.com/professional/index.html

Concerns regarding exogenous erythropoietin: safety

- Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)
- Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)
- Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)

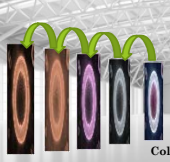


Singh, A. K. et al N Engl J Med 355(20):2085-98, 2006

Concerns regarding exogenous erythropoietin

- No oral form
  - Intravenous or subcutaneous
- Pure Red Cell Aplasia
- Hyperkalemia
  - Decreased clearance of potassium (-8.6%) due to the decrease in plasma volume – adjust clearances.
    - *Buur T., Lundberg M. Clin Nephrol 34(5): 230-5,1990.*
    - *Schaefer R. M., Schaefer, L. Nephrol Dial Transplant 11 Suppl 281-2, 1996*
- Hypertension
  - Rise of hematocrit and erythrocyte mass
  - Changes in production or sensitivity to endogenous vasopressors.
  - Alterations in vascular smooth-muscle ionic milieu
  - Dysregulation of production or responsiveness to endogenous vasodilatory factors
  - A direct vasopressor action of EPO
  - Arterial remodeling through stimulation of vascular cell growth.
    - *Vaziri, N. D. Am J Kidney Dis 33(5): 821-8, 1999.*

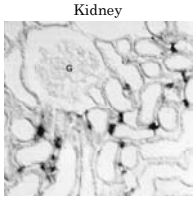
Bone marrow production "floor" for erythrocytes



Colony forming unit – stem cell: SCL, CBA alpha/beta, C-myb, HoxB4, LM2
Blast forming unit –erythroid: GATA-1
Colony forming unit erythroid: Epo/Epo receptor, W, SF, c-kit, IL-3, IL-6, IL-11, GM-CSFR
Reticulocyte
Erythrocyte

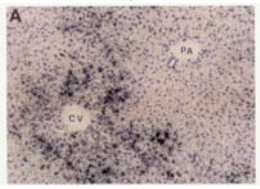
Where is erythropoietin produced?

Kidney



Bachmann, S. et al. J Histochem Cytochem 41(3): 335-341, 1993.

Liver

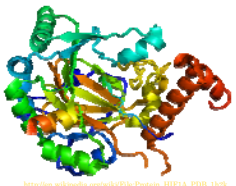


Koury S.T. et al. Blood 1991 77: 2497-2453.

- What regulates erythropoietin production?

Hypoxia inducible factor-1 (HIF) Regulates erythropoietin production

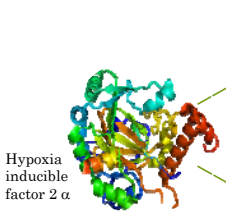
- There are three HIF-1 that regulate erythropoietin gene transcription
  - Hypoxia inducible factor 1 α
  - Hypoxia inducible factor 2 α
  - Hypoxia inducible factor 3 α
- HIF-2α is the dominant isoform in regulating erythropoietin production in humans.



http://en.wikipedia.org/wiki/File:Protein_HIF1A_PDB_1h2k.png

Percy MJ, et al. Blood 2008; 111:5400–02.
Percy MJ, et al. N. Engl. J. Med. 2008; 358: 162–8.

Regulation of Hypoxia Inducible Factor



NORMOXIA

- Degradation by Von Hipple Lindau Disease protein binding and ubiquination

HYPOXIA

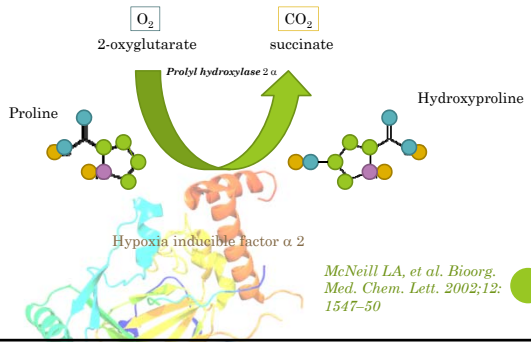
- Translocation to the nucleus, binding with HIF β, inducing the transcription of erythropoietin

Prolyl-Hydroxylases regulate HIF-1 fate

- Three prolyl hydroxylases
  - PHD1
  - **PHD2**
  - PHD3
- Ascorbate is required for function of the enzymes
  - Maintains iron in its reduced form
- These enzymes are inhibited by
  - Hypoxia
  - Iron
  - Cobalt

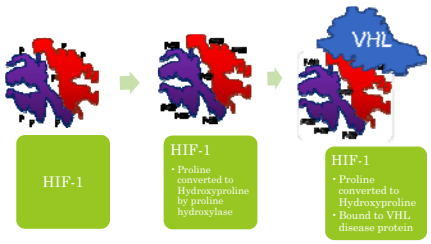
Epstein ACR, et al Cell 2001; 107: 43–54

Normoxia: prolyl hydroxylases



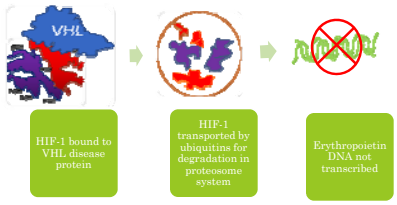
McNeill LA, et al. Bioorg. Med. Chem. Lett. 2002;12: 1547–50

NORMOXIA: HIF BONDING TO VON HIPPLE LINDAU DISEASE PROTEIN



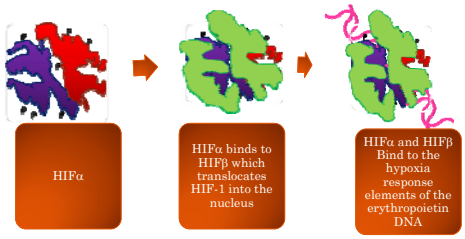
Ivan M, et al. Science 2001; 292: 464–8

NORMOXIA: NO ERYTHROPOIETIN TRANSCRIPTION



Salceda, S .et al. J Biol Chem 272(36): 22642-7, 1997.

HYPOXIA



Accelerators and Inhibitors of Erythropoiesis

Strategy 1: Block Inhibitors of Erythropoiesis:

HIF-2 +Prolyl-hydroxylase inhibitors

GABA

HCP

Fewer erythrocytes

Prolyl Hydroxylases Inhibitors (Anti-inhibitor)

- Polycythemia due to Prolyl hydroxylase gene defects
  - Gene defect of PHD2 in humans
    - *Percy MJ, et al. Proc. Natl. Acad. Sci. USA 2006; 103: 654–9.*
  - Gene defects of PHD1 and PHD3 in mice
    - *Minamishima YA, et al. Blood 2008; 111: 3236–44.*
    - *Takeda K, et al. Blood 2008; 111: 3229–35.*
  - Chuvash polycythemia
    - Ang SO, et al. Nat. Genet 2002; 32: 614–21.
- Inhibition of prolyl hydroxylase protein leads to an increase in erythropoietin production

Prolyl Hydroxylase Inhibitors

- Prolyl Hydroxylase Inhibitors
  - FibroGen and AstraZeneca
    - Developed oral medications based on small molecule inhibitors of hypoxia inducible factor-prolyl hydroxylase
      - FG 2216: no longer being studied due to a fatal case of hepatitis.
      - FG 4592 = Roxadustat
  - Daprodustat
  - Vadadustat
  - Molidustat
    - *Flamme I, et al. PloS One 2014; 9(11): e111838.*
  - Zyan1
    - Pharmacokinetic data in rat nephrectomy model
      - *Patel H, et al. Xenobiotica January 19, 2017, pages 1-8.*

Roxadustat: Phase 2 Trial

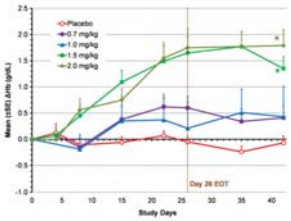


FIGURE 3: Mean change from BL in Hb (ΔHb) in TIW cohorts (EE population). Mean (SD) BL Hb was 10.1 (0.7) g/dL for roxadustat TIW subjects and 10.1 (0.6) g/dL for placebo subjects. Last-observation-carried-forward (LOCF) method was used to impute missing values. *P < 0.01 intergroup two-sample *t*-tests comparing roxadustat change from BL with placebo change from BL. End of treatment (EOT) for TIW was Day 26.

Besarab A, et al. Nephrol Dial Transplant 2015 30(10): 1665-73

Roxadustat: Erythropoietin Levels

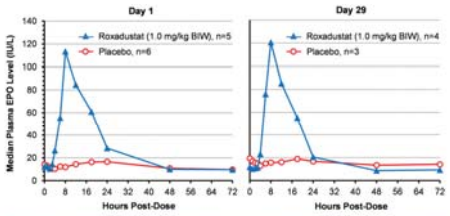


FIGURE 4: Changes in median plasma EPO on first and final days of treatment. Data are for the PK/PD population (subjects with complete dataset only).

Besarab A, et al. Nephrol Dial Transplant 2015 30(10): 1665-73

ROXADUSTAT: HEPCIDIN LEVELS FALL

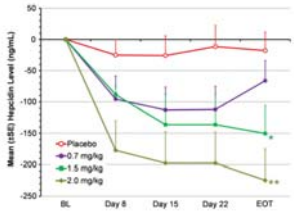


FIGURE 5: Mean change from BL in serum hepcidin (EE population). Data from BIW and TIW groups were pooled for each dose level. Serum hepcidin was not measured in the roxadustat 1.0 mg/kg dose group. LOCF method was used to impute missing data. *P = 0.048, **P = 0.0013, intergroup two-sample *t*-tests comparing roxadustat change from BL with placebo change from BL. EOT was Day 29 (BIW) or Day 26 (TIW).

Besarab A, et al. Nephrol Dial Transplant 2015 30(10): 1665-73

ROXADUSTAT: EFFECT WITHOUT IRON

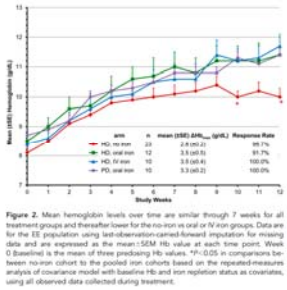


Figure 2. Mean hemoglobin levels over time are similar through 7 weeks for all treatment groups and thereafter lower for the no-iron vs oral or IV-iron groups. Data are for the EE population using last-observation-carried-forward imputation for missing data and are expressed as the mean ± SEM Hb value at each time point. Week 0 (baseline) is the mean of three predosing Hb values. *P<0.05 in comparisons between no-iron cohort to the pooled iron cohorts based on the repeated-measures analysis of covariance model with baseline Hb and iron repletion status as covariates, using all observed data collected during treatment.

Besarab A, et al. Nephrol Dial Transplant 2015 30(10): 1665-73

ROXADUSTAT: ADVERSE EVENTS

Table 3. AEs reported in three or more subjects

	Number of subjects with TEAE[a], *n* (%)	
	Roxadustat (*n* = 88)	Placebo (*n* = 28)
Any TEAE	52 (59.1)	13 (46.4)
Diarrhea	8 (9.1)	2 (7.1)
Headache	6 (6.8)	1 (3.6)
Back pain	4 (4.5)	1 (3.6)
Fatigue	4 (4.5)	0
Hyperkalemia	4 (4.5)	0
Peripheral edema	3 (3.4)	0
Dizziness	2 (2.3)	2 (7.1)
Insomnia	2 (2.3)	1 (3.6)
Seasonal allergy	1 (1.1)	2 (7.1)
Urinary tract infection (UTI)[b]	1 (1.1)	3 (10.7)

Besarab A, et al. Nephrol Dial Transplant 2015 30(10): 1665-73

ROXADUSTAT: INITIAL DOSE AND DOSE ADJUSTMENT

Table 2. Roxadustat dose levels

Roxadustat Dose Levels	Low Weight (40–60 kg)	Medium Weight (>60–90 kg)	Heavy Weight (>90–140 kg)
1 (initial dose)	60 mg 1.0–1.5 mg/kg	100 mg 1.1–1.7 mg/kg	140 mg 1.0–1.6 mg/kg
2	100 mg 1.7–2.5 mg/kg	140 mg 1.6–2.3 mg/kg	200 mg 1.4–2.2 mg/kg
3	140 mg 2.3–2.5[a] mg/kg	200 mg 2.2–2.5[a] mg/kg	300 mg 2.1–2.5[a] mg/kg

Dose adjustments for Hb response: if Hb was <11.0 g/dl and the rate of rise of Hb was <1.0 g/dl in the previous 4 weeks, the roxadustat dose was escalated up one dose level. The maximum allowed dose was 2.5 mg/kg. If Hb was >13.0 g/dl or rate of rise of Hb was ≥2.0 g/dl in the previous 4 weeks (excessive response), the roxadustat dose was reduced by one dose level, or by approximately 30% if the patient was at dose level 1.
[a]Roxadustat dose subject to a maximum of 2.5 mg/kg thrice weekly.

Besarab A, et al. J Am Soc Nephrol 2016; 27(4): 1225-33.

ROXADUSTAT VERSUS ERYTHROPOIETIN

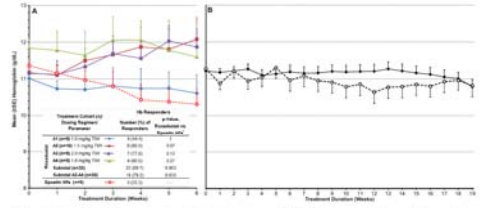


Figure 2. Hemoglobin levels over time (6 weeks) by treatment group. (A) Hb levels over time by dose cohort for participants randomly assigned to 6 weeks of treatment in part 1. Hb level responders are defined as the number (percent) of patients whose Hb levels did not decrease by >0.5 g/dL from their baseline (primary efficacy end point in part 1). (B) Least squares mean Hb levels over time (19 weeks), roxadustat-treated versus epoetin alfa–treated patients. Closed diamonds are roxadustat (n = 61); open circles are epoetin alfa (n = 22). *P values are from Fisher exact test (2 sided) comparing roxadustat with epoetin alfa. Error bars signify standard error (SE) of the mean.

Provenzano R, et al. Am J Kidney Dis. 2016;67(6):912-924

ROXADUSTAT: DOSING UNAFFECTED BY CRP

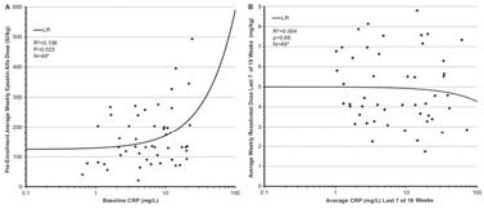
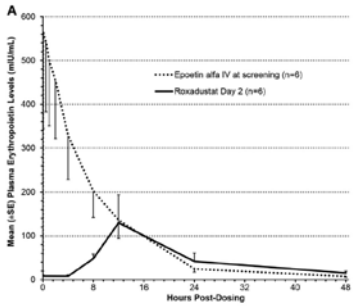


Figure 3. Baseline C-reactive protein (CRP) levels are correlated with (A) pre-enrollment epoetin alfa but not (B) roxadustat maintenance dose requirements. *N = 49: all participants randomly assigned to 19 weeks of roxadustat treatment and dosed beyond 12 weeks (maintenance phase) with valid baseline epoetin alfa dose data and valid baseline and average last 7 of 19 weeks of CRP data. Thus, this analysis did not include the 9 patients discontinued from roxadustat treatment for lack of efficacy (see Fig S1). Baseline CRP level was the average of the last 3 values prior to the first dose of study drug. CRP is plotted on the x-axis using a logarithmic scale. Abbreviation: LR, linear regression.

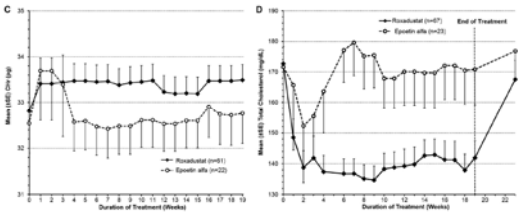
Provenzano R, et al. Am J Kidney Dis. 2016;67(6):912-924

ROXADUSTAT: PHARMACOKINETICS



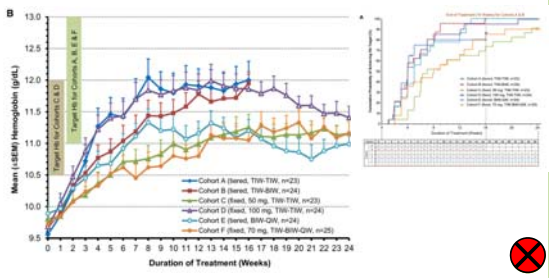
Provenzano R, et al. Am J Kidney Dis. 2016;67(6):912-924

ROXADUSTAT: IRON AND CHOLESTEROL



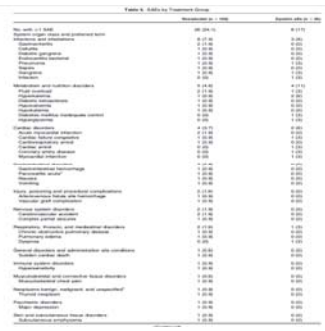
Provenzano R, et al. Am J Kidney Dis. 2016;67(6):912-924

ROXADUSTAT TREATMENT IN CKD



Provenzano R et al. Clin J Am Soc Nephrol 2016; 11: 982–991

ROXADUSTAT: ADVERSE EFFECTS

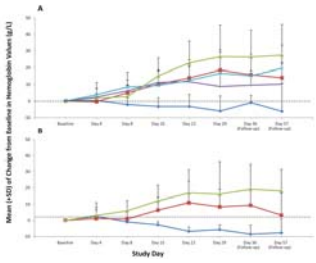


Provenzano R, et al. Am J Kidney Dis. 2016;67(6):912-924

Provenzano R et al. Clin J Am Soc Nephrol 2016; 11: 982–991

DAPRODUSTAT (GSK1278863)

- Adult subjects were either CKD stage 3-5 or were receiving hemodialysis.
- Randomly assigned patients reported to the clinical research unit for assessments and dosing on days 1, 4, 8, 15, and 22 (dosing days) and days 29, 36, and 57.
- They self-administered the study medication daily between the clinical research unit visits until day28.



Akizawa T, et al. Am J Nephrol 2017;45:127–135

DAPRODUSTAT (GSK1278863)

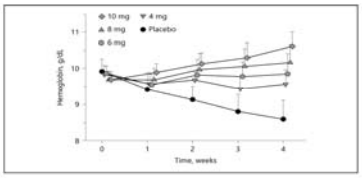


Fig. 2. Mean hemoglobin changes over time (intent-to-treat population; mean ± SD).

- Subjects previously treated with erythropoietin, stratified by baseline hemoglobin (<9.5 and≥ 9.5 g/dL), were randomized 1: 1:1: 1:1 to receive in double-blind fashion either 4, 6, 8, or 10 mg of Daprodustat or placebo orally once daily.
- Stopping criteria based on hemoglobin were any of the following: <7.5, ≥ 13.0, or a change >2 g/dL over 2 weeks for patients with hemoglobin ≥ 7.5 and <13 g/dL.
- Daprodustat 4–10 mg once daily produced moderate dose-dependent increases in hemoglobin over the 4-week treatment period relative to placebo.

Akizawa T et al. Amer J Nephrol 2017; 45: 127-135.

VADADUSTAT (AKB 6548)

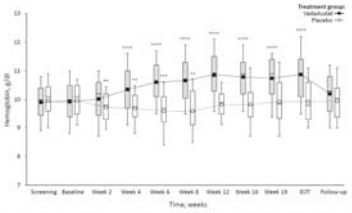


Figure 1| Mean hemoglobin level over time (modified intent-to-treat population). Box-and-whiskers plot represents 10th, 25th, 75th, and 90th percentiles. The medians are indicated by the line within the boxes, and the means are indicated by the symbol within the boxes. Comparison of baseline to weekly and end of treatment (EOT) means for vadadustat or placebo groups was performed with a 2-sided Student *t*-test at $\alpha = 0.05$; *P < 0.01; ***P < 0.001; ****P < 0.0001.

- 20-week, phase 2b multicenter, randomized, double-blind, placebo-controlled study to assess the ability of oral, once-daily Vadadustat to correct anemia in patients with NDD-CKD. Patients with NDD-CKD stages 3a/b, 4, and 5

Pergola PE, et al. Kidney International 2016; 90, 1115–1122

VADADUSTAT

Table 3| AEs and SAEs in the ITT population

Category	Number of patients, *n* (%) Vadadustat *n* = 138	Placebo *n* = 72
Patients with ≥1AE[a]	103 (74.6)	53 (73.6)
Diarrhea	14 (10.1)	3 (4.2)
Nausea	14 (10.1)	3 (4.2)
Constipation	5 (3.6)	4 (5.6)
Gastrointestinal hemorrhage	0 (0.0)	4 (5.6)
Fatigue	12 (8.7)	5 (6.9)
Edema peripheral	10 (7.2)	7 (9.7)
Urinary tract infection	9 (6.5)	6 (8.3)
Upper respiratory tract infection	2 (1.4)	5 (6.9)
Hyperkalemia	7 (5.1)	0 (0.0)
Headache	8 (5.8)	2 (2.8)
Dizziness	7 (5.1)	3 (4.2)
Renal failure acute	10 (7.2)	4 (5.6)
Renal failure chronic	7 (5.1)	3 (4.2)
Dyspnea	6 (4.3)	4 (5.6)
Hypertension	11 (8.0)	2 (2.8)
Hypotension	6 (4.3)	4 (5.6)
Patients with >1 SAE	33 (23.9)	11 (15.3)
Patients with >1 drug-related SAE	3 (2.2)	0 (0.0)
Patients with any renal- and/or dialysis-related AE	18 (13.0)	9 (12.5)
Patients with any renal-related SAE	13 (9.4)[a]	2 (2.8)
Patients with events that required dialysis	11 (8.0)	7 (9.7)
Patients with AEs leading to study withdrawal	10 (7.2)	3 (4.2)
Deaths	3 (2.2)	0 (0.0)

AE, adverse event; ITT, intent-to-treat; SAE, serious adverse event.
[a]Listed are AEs that were reported in ≥5% of the patients.

Pergola PE, et al. Kidney Int 2016; 90(5):1115-1122

CONCERNS REGARDING PROLYL HYDROXYLASE INHIBITORS

- Activating HIF and such hydroxylase inhibitors seem to closely mimic the gene expression response to hypoxia.
- More hypertension?
  - HIF-2α inhibitors were thought decrease systemic blood pressure because of increased HIF-1α-induced NO release in the vasculature. Real world experience?
- May impact mitochondrial metabolism, cellular growth and differentiation, angiogenesis and anaerobic metabolism.
- Unclear role in pathogenesis of cancer
- Unexpected adverse effects may yet be seen when used in more subjects/patients
- No pediatric data

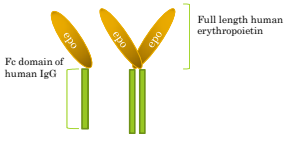
Strategy 2: Increase Accelerators of Erythropoiesis

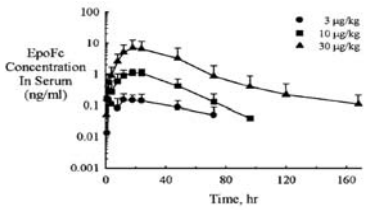
Continuous Erythropoietin Receptor Activator (CERA) Methoxy Polyethylene Glycol-Epoetin Beta (Mircera)

	AMICUS	ARCTOS	MAXIMA	PROTOS	STRIATA	RUBRA
Intervention	CERA IV 1x/2wk	CERA IV 1x/2wk	CERA IV 1x/2wk CERA IV 1x/4wk	CERA IV 1x/2wk CERA IV 1x/4wk	CERA IV 1x/2wk	CERA IV/SC pre-filled syringes 1x/2wk
Comparator	EPO IV 3x/wk	DAR SC 1x/wk	EPO IV 1-3x/wk	EPO IV 1-3x/wk	DAR IV 1x/wk or 1x/2wk	EPO IV/SC 1-3x/wk
Subjects	N=181 dialysis EPO-naïve	N=324 pre-dialysis EPO-naïve	N=673 dialysis	N=673 dialysis	N=313 dialysis	N=336 dialysis
Mean baseline Hgb	CERA: 9.4 g/dL EPO: 9.4 g/dL	CERA: 10.2 g/dL DAR: 10.2 g/dL	CERA 1x/2wk: 12.0 g/dL CERA 1x/4wk: 11.9 g/dL EPO: 12.0 g/dL	CERA1x/2wk: 11.7 g/dL CERA1x/4wk: 11.6 g/dL EPO: 11.6 g/dL	CERA: 12.0 g/dL DAR: 11.9 g/dL	CERA: 12.0 g/dL DAR: 11.9 g/dL
Mean Hgb Result	CERA: 12.1 g/dL EPO: 12.0g/dL	CERA: 12.3 g/dL DAR: 12.2 g/dL	CERA 1x/2wk: 11.9 CERA 1x/4wk: 11.9 g/dL EPO: 11.9 g/dL	CERA 1x/2wk: 11.7 g/dL CERA 1x/4wk: 11.5 g/dL EPO: 11.5 g/dL	CERA: 12.1 g/dL DAR: 11.8 g/dL	CERA: 11.9 g/dL EPO: 11.8 g/dL

Adapted from http://www.cadth.ca/media/pdf/E0025_Mircera_for_Renal_Anemia_cetap_e.pdf

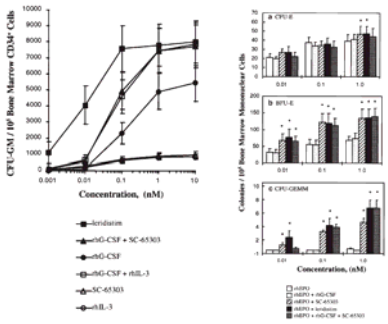
EPO Fc: After Single Inhalation





A.J. Bitonti, J.A. Dumont . Advanced Drug Delivery Reviews, 58, 1106–1118, 2006.

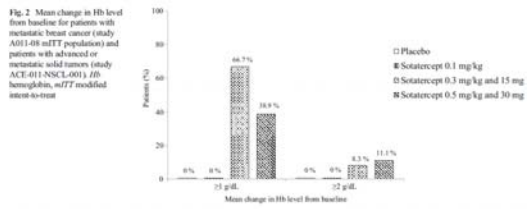
LERIDISTIM: EFFECTIVELY INCREASES CFU-E AND BFU-E



- A combination of erythropoietin (rhEPO) and leridistim resulted in greater numbers of BFU-E, CFU-GEMM and CFU-Mk than rhEPO alone.

Abegg AL et al. Leukemia 2002; 16, 316–326

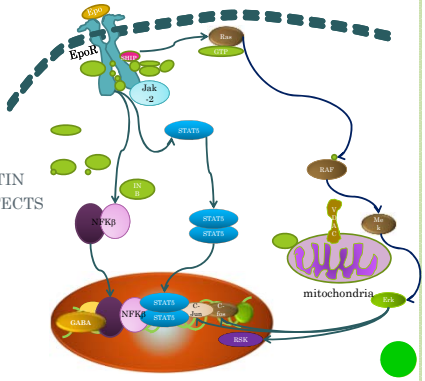
SOTATERCEPT



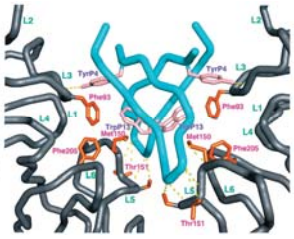
- Sotatercept is a recombinant fusion protein of human activin receptor type IIA (ActRIIA) and the fragment crystallizable (Fc) domain of the human immunoglobulin G1 antibody.
- Traps growth differentiation factor (GDF)-11, a ligand that binds to ActRIIA and impedes terminal erythroid maturation.
- May be safer in patients with cancer.

Raftopoulus H, et al. Support Care Cancer 2016; 24:1517–1525

ERYTHROPOIETIN RECEPTOR EFFECTS



Erythropoeitin mimetic peptides (EMP): Tricking the erythropoietin receptor?



- *Middleton SA, et al The Journal of Biological Chemistry 1999; 274 (20): 14163-14169*

- EMP dimers, consisting of two EMPs joined via a linker, have been shown to exhibit significantly improved activity compared to the corresponding monomers, with potency approaching that of the native hormone.
- Evaluation of the resulting molecules indicated a clear effect of PEG linker size on activity.
  - *Vadas O. et al. Biopolymers 90 (4): 496-502, 2008*

Peginesatide: A PEGylated dimeric peptide

Table 1 Summary of peginesatide studies in non dialysis requiring CKD patients

	PEARL 1			PEARL 2		
	Peginesatide 0.04 mg/kg	Peginesatide 0.025 mg/kg	Darbepoetin 0.75 µg/kg	Peginesatide 0.04 mg/kg	Peginesatide 0.025 mg/kg	Darbepoetin 0.75 µg/kg
Patients (n)	165	161	164	163	167	163
Change in Hb g/dL* (mean ± SD)	1.39 ± 0.87	1.64 ± 0.97	1.37 ± 0.86	1.50 ± 0.90	1.68 ± 0.96	1.35 ± 1.00
Difference in Hb versus darbepoetin group, mean (97.5% CI)**	0.03 (-0.19 to 0.26)	0.26 (0.04-0.48)		0.14 (-0.09 to 0.36)	0.31 (0.08 to 0.54)	
Transfusion (% of patients)	6.2%	7.3%	4.9%	11.4%	10.4%	4.9%

Note: *Changes in Hb levels from baseline to mean level during 12-week evaluation period; **noninferiority criteria.
Abbreviations: CI, confidence interval; Hb, hemoglobin; SD, standard deviation; CKD, chronic kidney disease.

Table 2 Summary of peginesatide studies dialysis requiring CKD patients

	EMERALD 1		EMERALD 2	
	Peginesatide group	Epoetin group	Peginesatide group	Epoetin group
Patients (n)	445	248	488	237
Change in Hb, g/dL* (mean ± SD)	-0.24 ± 0.94	-0.09 ± 0.92	-0.07 ± 1.01	-0.17 ± 1.00
Difference in Hb versus epoetin group, mean (95% CI)**	-0.15 (-0.30 to -0.01)		0.10 (-0.05 to 0.26)	
Transfusion (% of patients)	10.3%	8.6%	7.7%	9.9%

Notes: *Changes in Hb level from baseline to mean level during the 12-week evaluation period; **noninferiority criteria.
Abbreviations: CI, confidence interval; Hb, hemoglobin; SD, standard deviation; CKD, chronic kidney disease.

- 13 case reports of anaphylactic reactions secondary to administration of peginesatide, three of which resulted in death.
- In February 2013, the drug manufacturer voluntarily recalled the drug.
- *Kaushik T and Yaqoob MM Biologics: Targets and Therapy 2013; 7: 243-246*

Hematide™

- Single-group open-label trial
- Patients had chronic kidney disease and pure red-cell aplasia or hypoplasia due to anti-erythropoietin antibodies.
- Subcutaneous injection of Hematide™ 0.05 mg per kilogram every 4 weeks.
- The primary end point was a hemoglobin concentration above 11 g/dl, without the need for transfusions.
- 14 patients were treated with the Hematide™ for a median of 28 months.

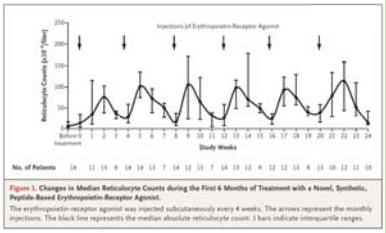


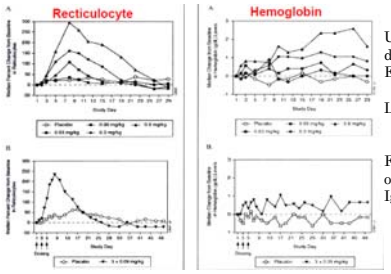
Figure 1. Changes in Median Reticulocyte Counts during the First 6 Months of Treatment with a Novel, Synthetic, Peptide-Based Erythropoietin-Receptor Agonist.
The erythropoietin-receptor agonist was injected subcutaneously every 4 weeks. The arrows represent the monthly injections. The black line represents the median absolute reticulocyte count. I bars indicate interquartile ranges.

Macdougall, I. C. et al. N Engl J Med 361: 19: 1848-55, 2009.

AGEM400

- Dimeric erythropoietin mimetic protein conjugated to hydroxyethylstarch.
- In vitro study
  - Efficiently stimulated erythropoiesis in vitro and efficiently stimulated survival of EPO-dependent cell line
  - **AGEM400(HES) was shown to have weak or absent effects on survival of, and signaling in, three different EPO-responsive hematopoietic cell lines.**
  - AGEM400 inhibited the activity of EPO. There was binding competition between EPO and AGEM400
  - *Kessler C, et al. Cytokine 2012; 57(2):226-237.*

CNTO 530: PHASE 1 STUDY



Bugelski PJ et al. J Biotechnol, 2008, 134, 171–180.
Bouman-Thio E et al. J Clin Pharmacol. 2008 ,48,1197-207

ESA SCORECARD

	Exogenous erythropoietin	Prolyl Hydroxylase Inhibitors	Erythropoietin receptor agonists
COST	+++	++	?
ROUTE	IV or SQ	Oral	SQ/Inhaled
Frequency	EPO 3x/week Darbepoetin 1x/1-2 weeks	2-3 times per week	2-4 weeks
Adverse effect profile	HTN, Hyperkalemia	Nausea, headache, hypertension, others?	HTN
Benefits	Known performer	Better iron absorption	Less frequent dosing


THANK YOU!
Watch for new ESA's!
Please contact me at ryyang1@ucsd.edu for any questions!