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Reason for report:

INITIATION

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FIBROGEN, INC.

Late-Stage Story with Transformative Potential in a Large Market; Initiate OP

- Bottom Line:** We are initiating coverage of FGEN with an Outperform rating and price target of \$52. FGEN is a leader in developing novel agents targeting fibrosis and hypoxia pathways for the treatment of anemia and fibrotic diseases.
- Lead candidate roxadustat** has a potential to be a transformative product in a large market. Roxadustat, a first-in-class prolyl-hydroxylase (PHD) inhibitor, mimics the body's natural response to hypoxia (low oxygen) conditions and has been shown in a large Phase II program involving nearly 1,300 patients to be safe and effective in treating anemia in patients with chronic kidney disease (CKD). Erythropoietin-stimulating agents (ESAs), the current mainstay for the anemia market still generate sales of ~\$8-9B despite significant limitations including cardiovascular (CV) safety concerns. Unlike ESAs, roxadustat is an oral agent that 1) raises hemoglobin (Hb) without causing supraphysiologic elevations in endogenous erythropoietin, 2) reduces the need for IV iron by through the suppression of hepcidin, 3) is effective in incident dialysis patients and hypo-responders to ESAs without requiring a high dose, 4) lowers LDL and total cholesterol, and 5) does not raise blood pressure. Consistent with MEDACorp key opinion leader (KOLs) feedback, we think roxadustat has the potential to be a "game changer" in the large anemia market.

- The key investor concerns** appear to be whether roxadustat is safe and whether there are safety liabilities associated with PHD inhibition and stabilizing hypoxia-inducible factor (HIF). While it is impossible to exclude cancer or CV risks associated with PHD inhibition, we believe the preponderance of scientific and clinical evidence suggests that the risk is not high. The data points include infrequent cancers associated with HIF activating mutations and large epidemiology studies showing low oxygen conditions at high altitude are associated with reduced cancer and CV risks as well as clean preclinical and clinical data to date. Also, we believe available data also strongly suggest that high levels of ESAs, not increased Hb levels, are responsible for elevated CV risks from ESA use. We think roxadustat has a good chance to show reduced risks in cardiovascular outcomes relative to ESAs in its ongoing Ph III trials.

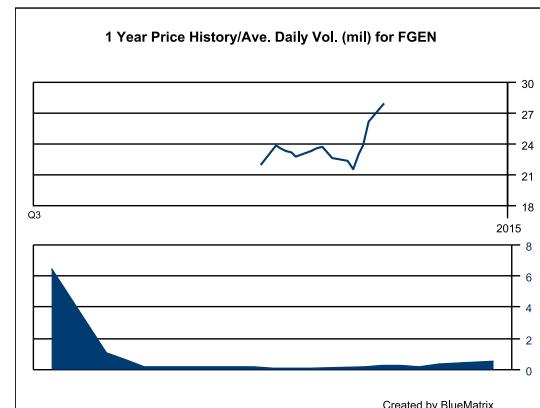
- We believe FibroGen is employing the right strategy in targeting the rapidly growing Chinese market.** FGEN is taking a unique development approach in China using the "Green Channel", which could potentially allow the company to gain access to the country's rapidly expanding dialysis population.

- A source of potentially large upside may be the wholly owned anti-fibrotic compound.** FG-3019 is a CTGF inhibitor in Ph II development for a number of fibrotic indications, has shown a unique ability to reverse fibrosis. We believe there is limited valuation associated with this asset

Key Stats:

(NASDAQ:FGEN)

S&P 600 Health Care Index:	1,398.07
Price:	\$28.00
Price Target:	\$52.00
Methodology:	DCF & sum of the parts using probability weighted revenues and 10% discount rate
52 Week High:	\$30.15
52 Week Low:	\$20.10
Shares Outstanding (mil):	56.7
Market Capitalization (mil):	1,587.6
Book Value/Share:	0.43
Cash Per Share:	\$5.43
Net Debt to Total Capital:	0%
Dividend (ann):	\$0.00
Dividend Yield:	0.0%



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2013A	--	--	--	--	\$102.2	--	--	--	--	(\$0.25)	NM
2014E	\$53.9A	\$53.9A	\$13.6A	\$20.0	\$141.5	\$0.26A	\$0.26A	(\$0.67)A	(\$0.62)	(\$0.84)	NM
2015E	--	--	--	--	\$202.0	--	--	--	--	(\$0.80)	NM

Source: Company Information and Leerink Partners LLC Research
 Revenues in \$M; GAAP EPS presented; IPO 11.13.14

Please refer to Pages 102 - 104 for Analyst Certification and important disclosures. Price charts and disclosures specific to covered companies and statements of valuation and risk are available at <https://leerink2.bluematrix.com/bluematrix/Disclosure2> or by contacting Leerink Partners Editorial Department, One Federal Street, 37th Floor, Boston, MA 02110. Rx trends derived from IMS Health.

in the stock; therefore we think it represents a low-priced call option with large upside.



FIBROGEN

December 9, 2014

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Investment Thesis

- **Bottom Line:** We are initiating coverage of FGEN with an Outperform rating and price target of \$52. FGEN is a leader in developing novel agents targeting fibrosis and hypoxia pathways for the treatment of anemia and fibrotic diseases.
- **Lead candidate roxadustat has a potential to be a transformative product in a large market.** Roxadustat, a first-in-class prolyl-hydroxylase (PHD) inhibitor, mimics the body's natural response to hypoxia (low oxygen) conditions and has been shown in a large Phase II program involving nearly 1,300 patients to be safe and effective in treating both dialysis-dependent (DD) and non-dialysis dependent (NDD) chronic kidney disease (CKD). Erythropoietin-stimulating agents (ESAs), the current mainstay for the anemia market still generate sales of ~\$8-9B despite significant limitations including cardiovascular (CV) safety concerns. Unlike ESAs, roxadustat is an oral agent that 1) raises hemoglobin (Hb) without causing supraphysiologic elevations in endogenous erythropoietin, 2) reduces the need for IV iron by through the suppression of hepcidin, 3) is effective in incident dialysis patients and hypo-responders to ESAs without requiring a high dose, 4) lowers LDL and total cholesterol, and 5) does not raise blood pressure. Consistent with MEDACorp key opinion leader (KOLs) feedback, we think roxadustat has the potential to be a "game changer" in the large anemia market.
- **The key investor concerns appear to be whether roxadustat is safe and whether there are safety liabilities associated with PHD inhibition and stabilizing hypoxia-inducible factor HIF as a result.** While it is impossible to exclude cancer or CV risks associated with PHD inhibition, we believe the preponderance of scientific and clinical evidence suggests that the risk is not high. The data points include infrequent cancers associated with HIF activating mutations and large epidemiology studies showing low oxygen conditions at high altitude are associated with reduced cancer and CV risks as well as clean preclinical and clinical data to date. Additionally, we believe available data also strongly suggest that high levels of ESAs, rather than increased Hb levels are responsible for elevated CV risks from ESA use. We believe roxadustat has a good chance to show reduced risks in cardiovascular outcomes relative to ESAs in its ongoing Phase III trials.
- **We believe that the company is employing the right strategy in targeting the rapidly growing Chinese market.** FGEN is taking a unique development approach in China using the "Green Channel", which could potentially allow the company to gain access to the country's rapidly expanding dialysis population.
- **A source of potentially large upside may be the wholly owned anti-fibrotic compound.** FG-3019 is a CTGF inhibitor in Ph II development for a number of fibrotic indications, has shown a unique ability to reverse fibrosis. We believe there is limited valuation associated with this asset in the stock; therefore we think it represents a low-priced call option with large upside.

Valuation

- Our valuation for FGEN is \$52 a share based on DCF and sum of the parts analysis. We include probability-weighted roxadustat royalties from Astellas (EU and Japan) and AZN (US and ROW) and the 50% roxadustat profit-share with AZN (MP) in China. For all territories, we assume a 70% probability of success for the dialysis-dependent chronic kidney disease (CKD) indication and a 60% probability of success for the non-dialysis dependent CKD indication. We assume a 10% discount rate, which believe is appropriate as given our probability-weighted sales. We currently assign \$300M valuation to FGEN's pipeline programs beyond roxadustat.

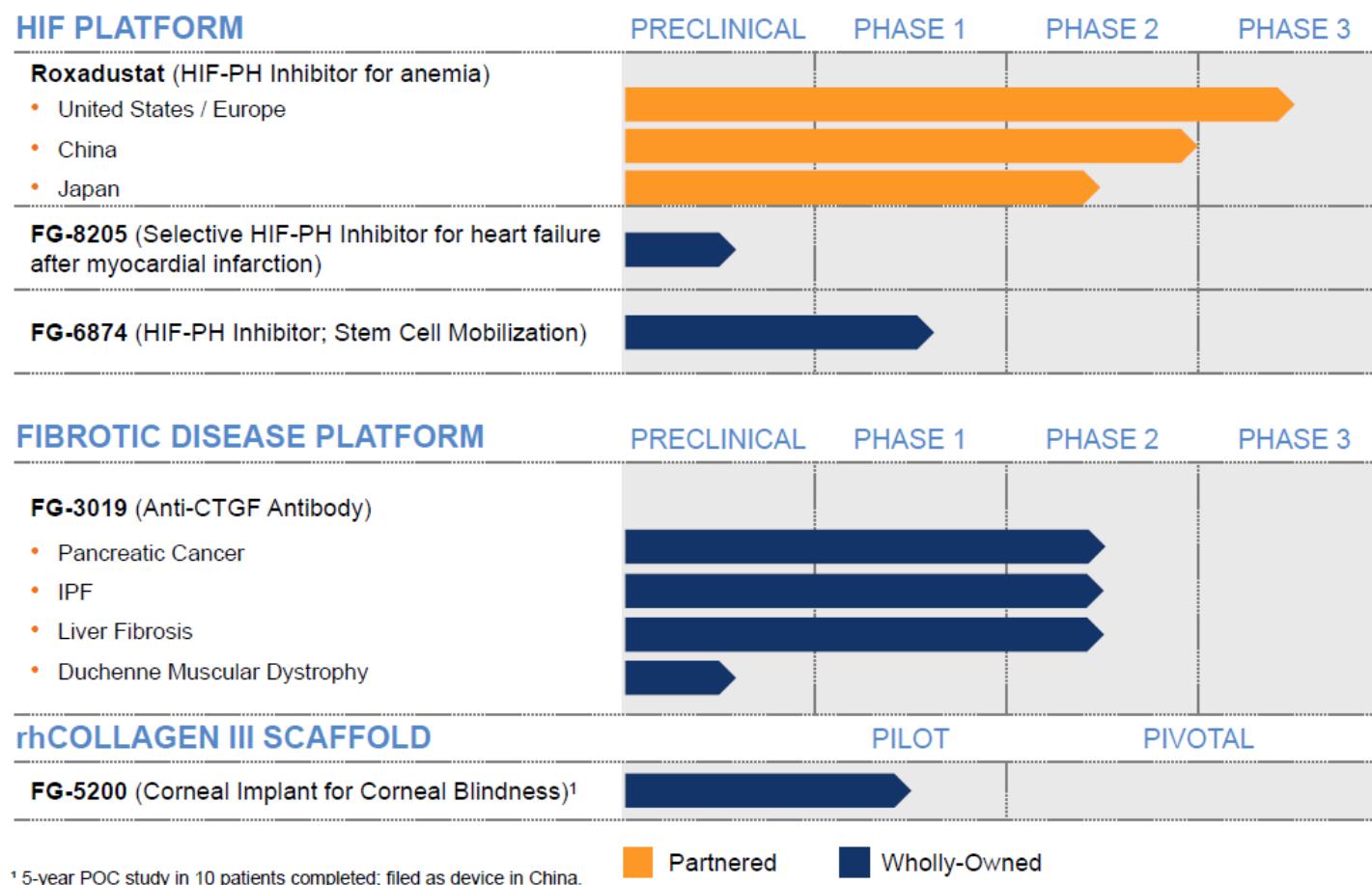
Risks to Valuation

- Clinical risks including ability for roxadustat to show a statistically significant improvement or clinically relevant trend towards improvement in cardiovascular (CV) outcomes versus erythropoietin-stimulating agents (ESAs) in its Phase III dialysis trials or placebo in its Phase III non-dialysis trials.
- Unknown safety issues associated with PHD inhibition or HIF stabilization.
- Clinical and regulatory risks associated with bringing a new class to the market in various territories, particularly in China.
- Uncertain size of the potential anemia market, particularly outside the dialysis setting.
- Unknown reimbursement landscape in the US regarding the inclusion of roxadustat in CMS's Prospective Payment System (aka, "The Bundle").
- Competition from other HIF-PH inhibitors

FibroGen Overview

- FibroGen is a leader in developing novel agents targeting hypoxia-inducible factor (HIF) pathway for the treatment of anemia and connective tissue growth factor (CTGF) for fibrotic diseases.
- Roxadustat (FG2592) is an inhibitor of HIF-prolyl hydroxylase (HIF-PH) which is currently in Phase III trials in the US and EU for the treatment of dialysis-dependent (DD) and non-dialysis dependent (NDD) chronic kidney disease (CKD). Large global Phase III program is expected to enroll 7,000-8,000 patients. Phase I/II enrolled 1,271 subjects. Initial Phase III data are expected in **2017**.
- The company expects to initiate Phase III trials of roxadustat in China in **1H:15**, with results in **2H:16**. As these studies will be smaller and shorter than the US/EU registrational trials, the agent could be approved in China first, potentially as early as **mid-2017**.
- FibroGen has established a wholly owned Chinese subsidiary to utilize the “green channel” for domestic manufacturers with innovative products
- FibroGen is partnered with Astellas in the EU, Japan, Commonwealth of Independent States (CIS), Middle East, and South Africa and with AZN in the US, China, and ROW.
 - FibroGen and AZN will split profits and commercialization and development costs ~50/50 in China.
 - Ex-China, FibroGen's development costs will be capped at \$116.5M and will earn royalties and transfer revenues from in the low-to-mid 20's on net product sales
- FG-3019 is a CTGF inhibitor is in Phase II development for a number of fibrotic indications, including IPF, pancreatic cancer, liver fibrosis, and potentially Duchene's Muscular Dystrophy (DMD; preclinical).
- Key financials: Total cash and investments at the end of September 2014 was **\$308M** (adjusted to include IPO proceeds).

Pipeline



- Roxadustat: Oral agent with potential to replace erythropoietin-stimulating agents (ESAs) for the treatment of anemia in chronic kidney disease (CKD; dialysis and non-dialysis), cancer (myelodysplastic syndrome [MDS], chemotherapy-induced anemia [CIA]), and other diseases.
- FG-3019: Anti-CTGF agent which has been shown to reverse fibrosis in some patients with IPF and shown dose-dependent improvements in survival when used in combination with erlotinib and gemcitabine.
- FG-5200: Biosynthetic cornea designed to address worldwide shortage of donor corneas

Catalysts and Events

Catalyst	Expected Timing
Roxadustat	
Initiate Phase III trials in China	1H:15
Complete enrolment in Phase III China trials	2H:15
Complete enrolment in Phase III US trials	1H:16
Phase III China data	2H:16
Possible China approval	mid-2017
Data for US Phase III NDD-CKD studies	2017
FG-3019	
Initiate Phase II trial in 1st-line pancreatic cancer (in combo with gemcitabine and Abraxane)	1H:15
Interim Phase II data in neoadjuvant pancreatic cancer (in combo with gemcitabine and Abraxane)	2H:15
Initiate Phase II trial in DMD	2015
Phase II data from HBV-associated liver fibrosis trial in Hong Kong and Thailand	2015
Initiate Phase II trial in liver fibrosis	2015
Phase II data from Study 067 in mild-to-moderate IPF	2H:16

Anemia Treatment Has
Undergone Dramatic
Recent Changes but Still
Represents a Large
Opportunity

US CKD/ESRD Anemia Market

- **Dialysis market:**
 - According to the 2013 US Renal Data System (USRDS) Annual Data Report, there were ~430K patients on either peritoneal or hemodialysis in 2011
 - KOLs indicate that almost all of these patients are ESAs

- **Non-Dialysis CKD market:**
 - According to FibroGen, there are currently 18.5M Stage 3-5 CKD patients not on dialysis in the US
 - 106K are considered “pre-dialysis” and treated by a nephrologist
 - 5.7M have CKD secondary to diabetes
 - 12.7M have CKD secondary to hypertension
 - 9.9% have hemoglobin levels <11 g/dL
 - 12% have hemoglobin levels between 11 and 12 g/dL

	NDD-CKD Nephrology	DM + CKD	HTN + CKD, no-DM	All NDD-CKD Stages 3-5
Non-Dialysis CKD 3-5 Prevalence (2011) [†]	106K	5.7 MM	12.7 MM	18.5MM
Anemia % (Hb<12g/dL)	53.4%	36.1%	15.4%	21.9%
Anemia % (Hb<11g/dL)	49.0%	17.3%	6.3%	9.9%

The CHOIR, CREATE, and TREAT trials showed that treating to higher hemoglobin (Hb) levels with ESAs led to no benefit, potentially harm

All three trials were conducted in CKD patients not yet on dialysis

- **CHOIR (Epogen/Procrit; 2006)**

- Showed higher rates of death and CV outcomes in patients treated to higher Hb levels (HR=1.34; p=0.03)

- **CREATE (Mircera; 2006)**

- Showed no difference in a composite endpoint of 8 CV events between the high- and low-Hb target groups
- However, time to initiation of dialysis after 18 months was shorter in the high Hb target arm (p=0.03).

- **TREAT (Aranesp; 2009)**

- Showed no difference in CV primary endpoints between the high- and low-Hb target arms among diabetic CKD patients
- The rate of stroke was higher in the high target Hb arm (HR=1.92; p<0.001)

Study	N (pts)	HB target (g/dL)	ESA	GFR range (mL/min/1.73 m ²)	Primary endpoint	P value for primary endpoints
CHOIR (2006) [10]	603	13.5 versus 11.3	Epoetin Alfa	15–50	Death, MI, CHF, CVA	0.03 for composite favoring lower Hb
CREATE (2006) [22]	1432	13–15 versus 10.5–11.5	Epoetin Beta	15–35	Composite of 8 CV events, CKD progression	NS for CV events. 0.03 for ESRD favoring lower Hb group
TREAT (2009) [23]	4038	13 versus 9	Darbepoetin Alfa	20–60	Death, CV Event, ESRD	NS

In 1998, the Normal Hematocrit Trial (NHT) also showed an increase in death and non-fatal myocardial infarction (MI) among hemodialysis patients with CV disease

Table. Key Features of 4 Landmark Studies of Erythropoiesis-Stimulating Agents in Patients With Chronic Kidney Disease

	NHT		CREATE		CHOIR		TREAT	
ESA used	Epoetin alfa		Epoetin beta		Epoetin alfa		Darbepoetin alfa	
Inclusion criteria								
eGFR/Cl _{Cr} , mL · min ⁻¹ · 1.73 m ⁻²	NA (hemodialysis)		15–35		15–50		20–60	
Hemoglobin, g/dL	9–11		11–12.5		<11		≤11	
Other (selection)	Presence of ischemic heart disease or congestive heart failure, receiving ESA treatment		Absence of advanced cardiovascular disease, ESA naïve		Absence of unstable angina, ESA naïve		Presence of diabetes mellitus, no cardiovascular events and no ESA received in previous 12 wk	
Primary cardiovascular end point	Death or nonfatal MI		Earliest of sudden death, nonfatal MI, acute heart failure, stroke, TIA, complication of peripheral vascular disease (amputation or necrosis), angina, or cardiac arrhythmia with hospitalization for >24 h		Earliest of death, nonfatal MI, hospitalization for congestive heart failure, stroke		Earliest of death, nonfatal MI, congestive heart failure, stroke, hospitalization for myocardial ischemia	
Follow-up, median, mo	14		36 (Mean)		16		29	
Hemoglobin target, g/dL	9–11	13–15	10.5–11.5	13–15	11.3	13.5	Rescue at <9	13
Enrolled, n	615	618	302	301	717	715	2026	2012
Primary end point, n	164	202	47	58	97	125	602	632
Hazard ratio (P)	Referent	1.3 (NR)	0.78 (0.20)	Referent	Referent	1.34 (0.03)	Referent	1.05 (0.41)
95% confidence interval		0.9–1.9	0.53–1.14			1.03–1.74		0.94–1.17
Stroke (TIA), n	9	14	5 (1)	6 (5)	12	12	53	101
Hazard ratio (P)	NR		NR		Referent	1.01 (0.98)	Referent	1.92 (<0.001)
95% confidence interval						0.45–2.25		1.38–2.68

NHT indicates Normal Hematocrit Trial; CREATE, Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta; CHOIR, Correction of Hemoglobin and Outcomes in Renal Insufficiency; TREAT, Trial to Reduce Cardiovascular Events With Aranesp Therapy; eGFR, estimated glomerular filtration rate; Cl_{Cr}, creatinine clearance; ESA, erythropoiesis-stimulating agent; MI, myocardial infarction; NR, not reported; and TIA, transient ischemic attack.

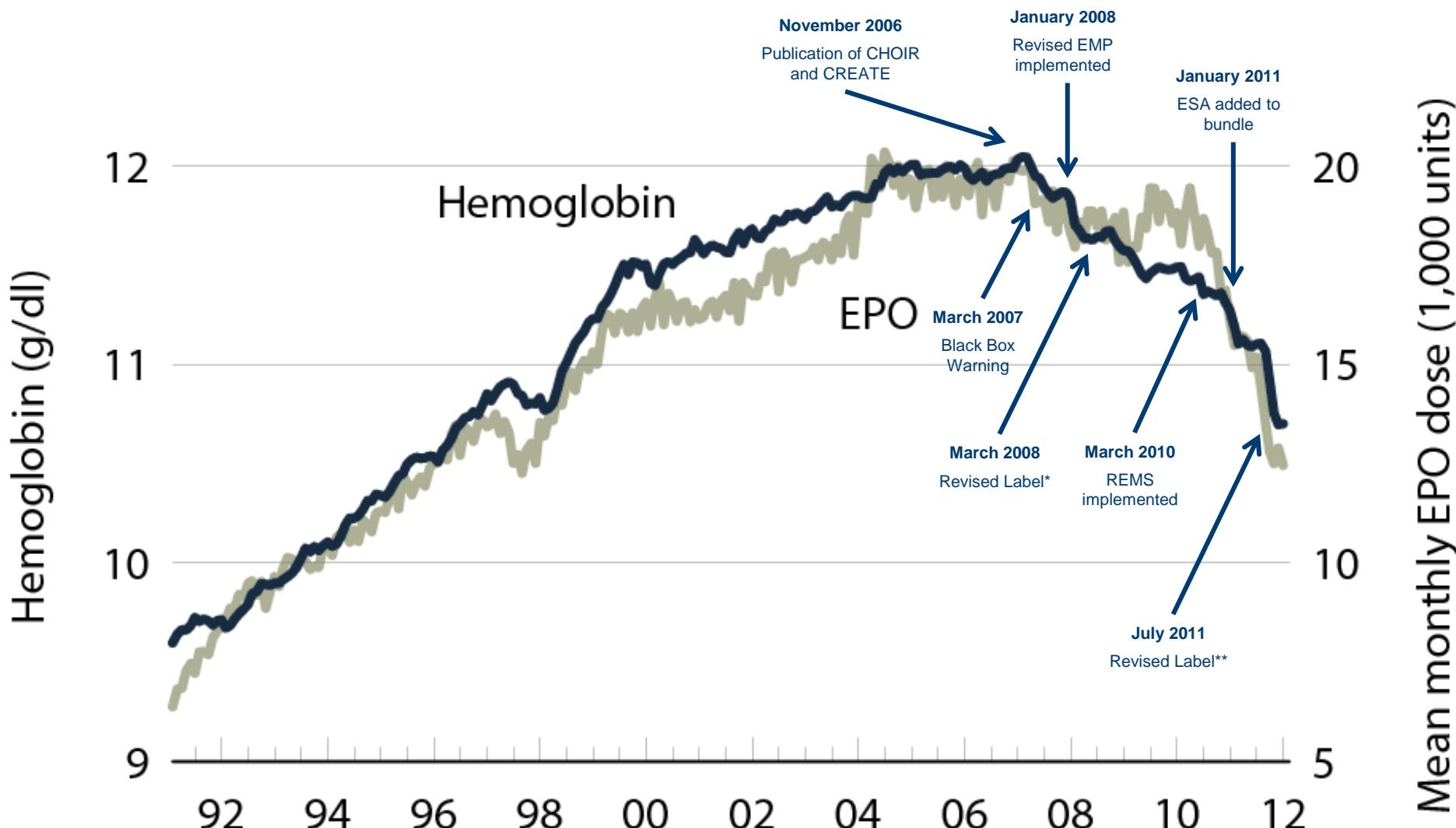
Further pressure has been put on the use of ESAs through CMS's Prospective Payment System (aka, "The Bundle")

In 2011, the Center for Medicare and Medicaid Services (CMS) instituted the ESRD Prospective Payment System (PPS), which paid a bundled rate per patient for all dialysis and dialysis-related treatments, including ESAs, vitamin D, IV iron, all ESRD lab tests, and oral medications with IV equivalents.

- Under this system, ESAs went from being a profit center (Average Sales Price [ASP] +6%) to a cost center.
- As part of the Bundle, the Quality Incentive Program (QIP) originally provided for a reduction in the payment amount to dialysis providers based on the percentage of patients whose Hb levels fell outside of the 10 to 12 g/dL range.
 - The 10 g/dL floor was removed in 2013
 - The 12 g/dL ceiling is scheduled to be removed in 2017
- Oral agents such as AMGN's Sensipar (cinacalcet) and phosphate binders were originally scheduled to become included in the bundle on January 1st, 2014; however this was delayed two years until January 1st, 2016 as a result of the American Taxpayer Relief Act of 2012. Inclusion of these oral agents was further delayed until 2024 as a result of the Protecting Access to Medicare Act of 2014.
 - The 2014 Act also required the Secretary of Health and Human Services (HHS) to develop a process by 2016 that determines when a drug is no longer considered an oral-only medication.

ESA use in dialysis has declined dramatically after a series of regulatory and labeling changes brought about by the publication of CHOIR and CREATE data

Mean monthly hemoglobin & mean EPO dose per week: hemodialysis patients



*Higher doses shorten survival and time to tumor progression

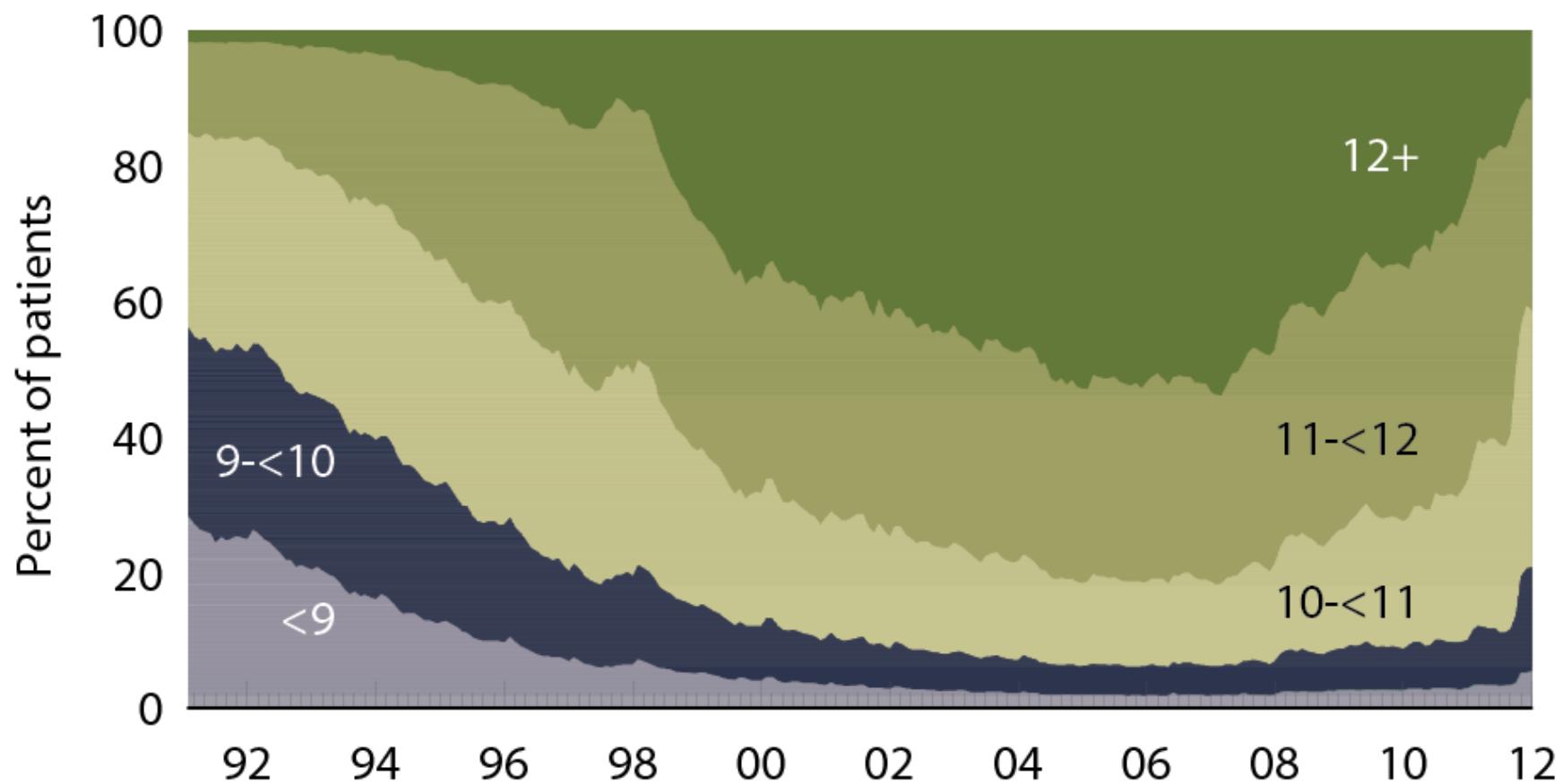
**Elevated risks above 11 g/dL, no dose that does not increase risks, use lowest dose sufficient to avoid RBC transfusions

EMP = Erythropoietin monitoring policy; REMS = Risk Evaluation and Mitigation Strategy

Source: USRDS 2013 ADR; 22.Spiegel et al., Am J Kidney Dis. 2010;55:113-120; company reports, Leerink Partners analysis

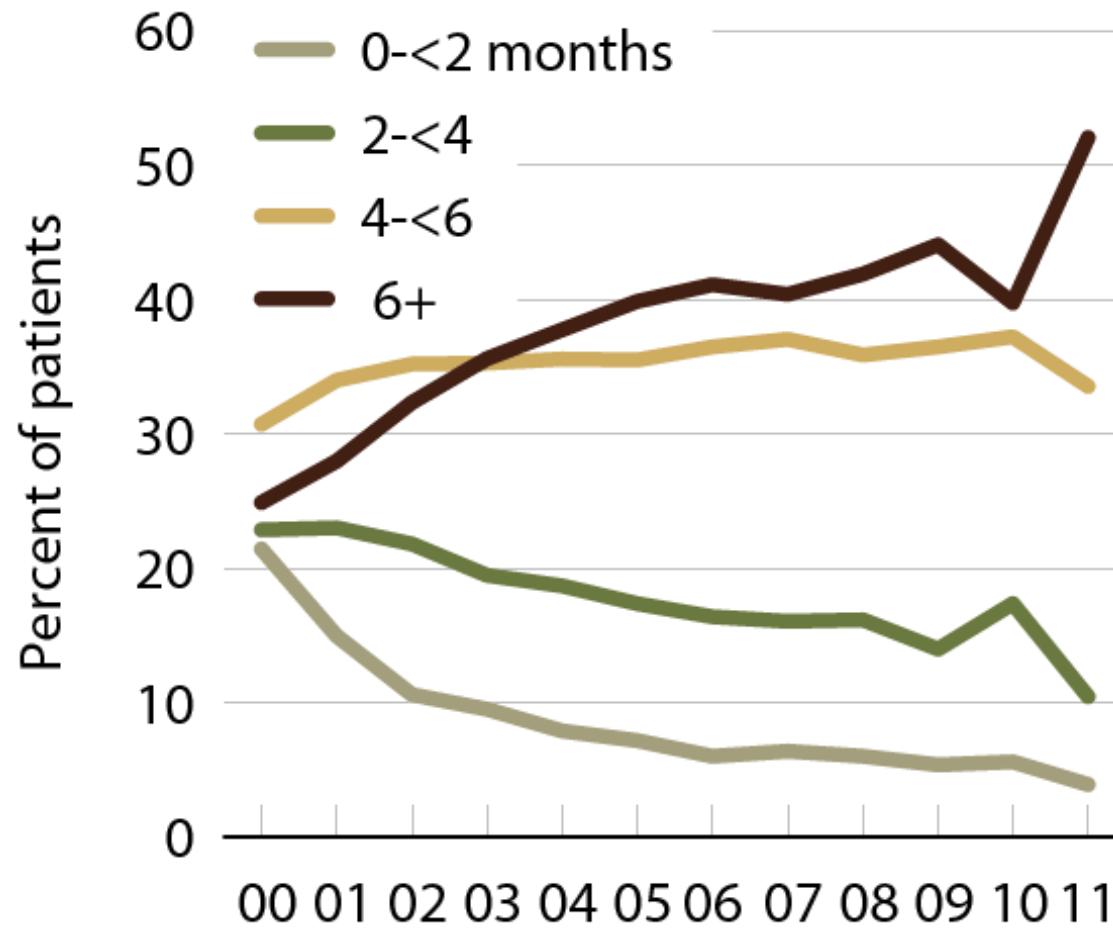
Over half of dialysis patients are currently treated to hemoglobin levels >11 g/dL

Patient distribution, by mean monthly hemoglobin (g/dL): hemodialysis patients



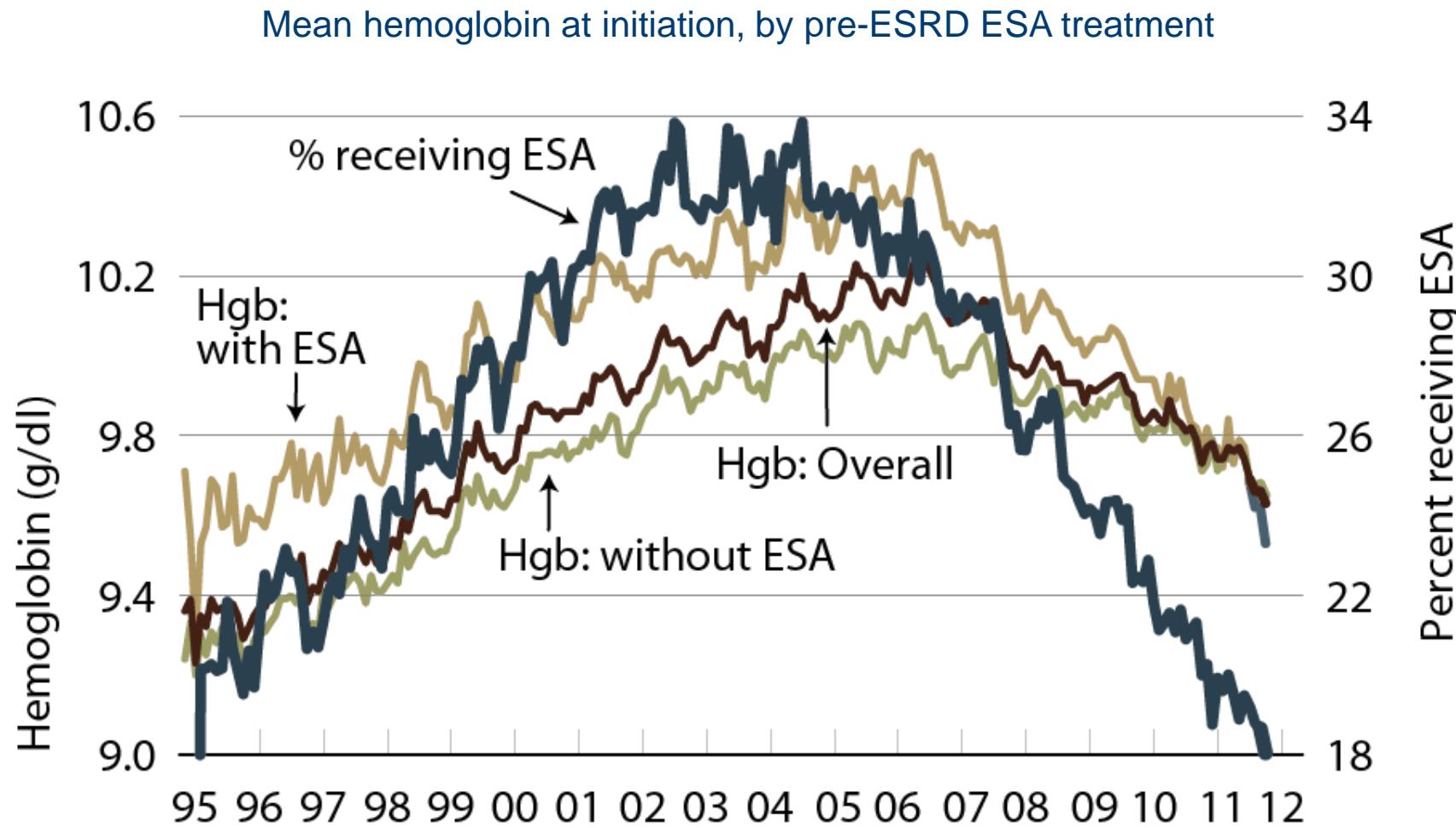
Use of IV iron has increased with lower ESA use in dialysis patients

Months with IV iron in the first six months of hemodialysis (EPO-treated patients)



Oral iron is typically not effective in dialysis patients receiving ESAs.

Use of ESAs have also declined in the Pre-Dialysis CKD market

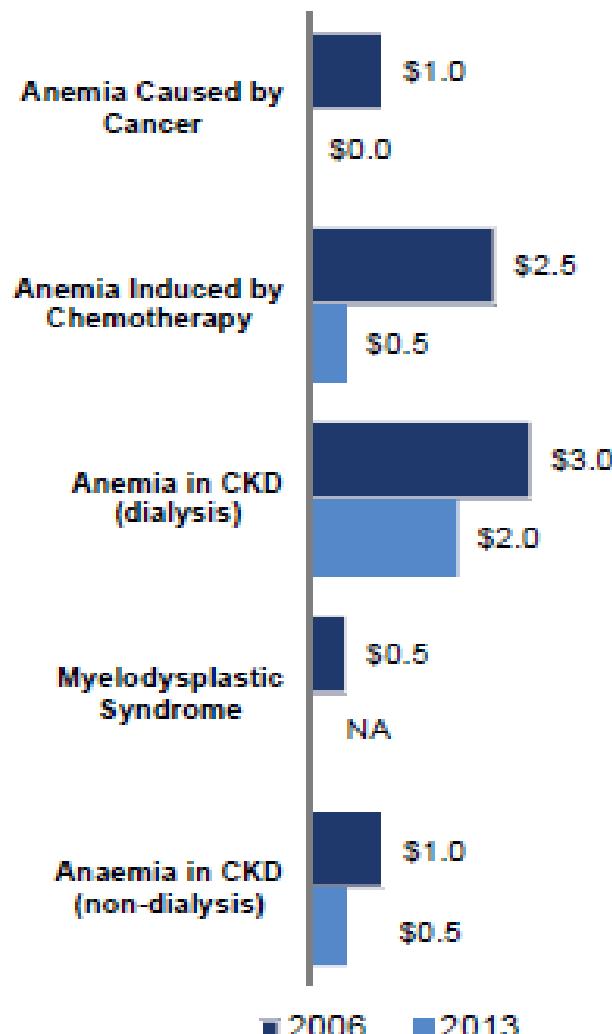


Anemia remains a large market opportunity despite declining sales of ESAs

- In 2006, sales of erythropoietin-stimulating agents (ESAs) totaled ~\$8B in the US across several anemia indications. However, as a result of several negative outcomes trials, label changes, and reimbursement decisions, sales have declined by ~50%.
 - Use of ESAs in anemia of cancer has ceased following a label change stating that these agents shortened overall survival and/or increased the risk of tumor progression or recurrence in several tumors
 - Use of ESAs in chemotherapy induced anemia has also declined sharply
 - In anemia of dialysis-dependent (DD) and non-dialysis dependent (NDD) chronic kidney diseases (CKD), use and average dose declined following the publication of the CHOIR and CREATE trials in late 2006.
- Epojen biosimilars could reach the US market beginning in 2015.
- **ESAs approved in US:**
 - AMGN's (MP) Epojen (epoetin alfa) - marketed for dialysis patients
 - JNJ's (OP) Procrit (epoetin alfa) - marketed for non-dialysis patients
 - AMGN's Aranesp (darbepoetin alfa)
 - Roche's Mircera (epoetin beta) – not yet launched in US
- **ESAs approved ex-US:**
 - JNJ's Eprex /Erypo
 - AMGN's Aranesp
 - Roche's Mircera
 - NVS's (OP) Binocrit (biosimilar epoetin alfa), TEVA's (OP) Eporatio (epoetin theta), HSP's Retacrit (epoetin zeta), 3SBio's Epiao (recombinant human erythropoietin), in China

Anemia remains a large market opportunity despite declining sales of ESAs

Approximate U.S. Sales (\$B)



Regulatory / Reimbursement Changes

Halt of ESA sales for anemia in cancer (2007)

Only one primary tumor type (SCLC¹) has adequate safety evidence (2008) REMS program (2010)

ESA restricted to Hb 10-11 g/dL after FDA rejects evidence supporting Hb 11 or higher (2011) Bundling (2011)

Sponsors are requested to obtain labeling (2010)

ESA use restricted to Hb < 10 g/dL, not to exceed Hb 10 g/dL and dose reduction when exceeded.

Limited to transfusion patients, and have allosensitization risk being eligible on transplant list

¹Small cell lung cancer

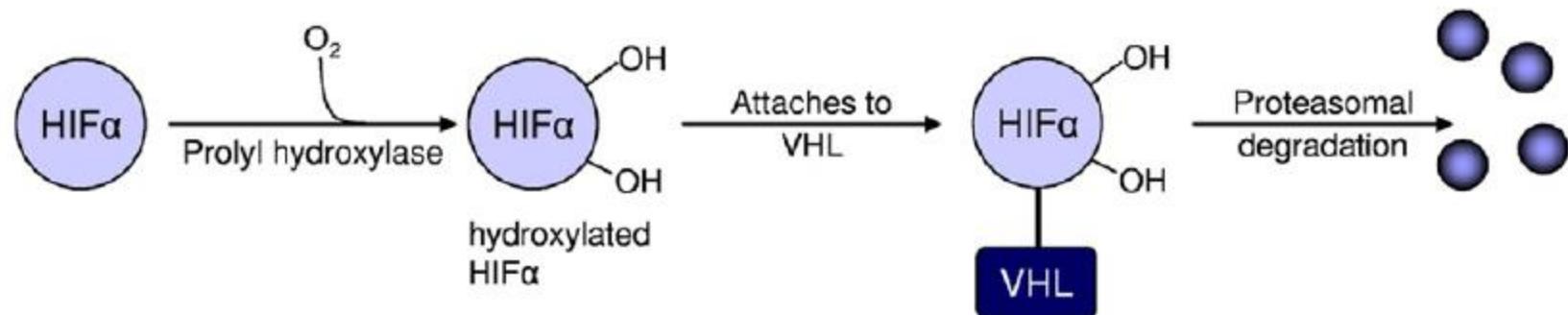
Roxadustat is a Potential “Game Changer”

Roxadustat Overview

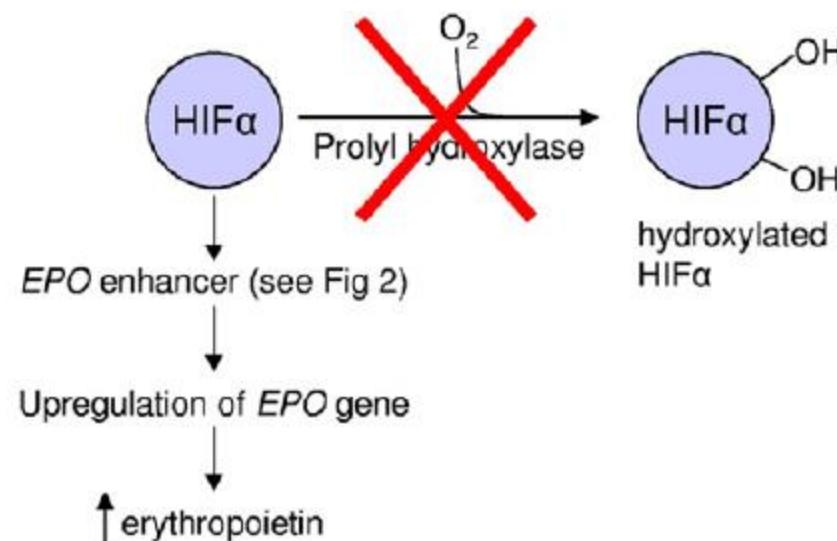
- Inhibits prolyl-hydroxylase (PH), preventing the degradation of hypoxia inducible factor (HIF)
 - Upregulates the production of EPO
 - Suppresses hepcidin, resulting in increased iron uptake in the intestines and release of cellular iron into the blood
- Potential benefits of roxadustat:
 - Raises hemoglobin by increasing endogenous EPO within or near physiologic levels
 - This may improve safety compared to ESAs, which raise EPO to supraphysiological levels
 - Effective in patients who are hyporesponsive to ESAs due to ability to lower hepcidin
 - Increased uptake of iron the intestines allows for use of oral iron (instead of IV)
 - In some patients, the release of cellular iron from internal storage may eliminate the need for iron therapy
 - Oral dosing offers more convenience for non-dialysis patients and potential reimbursement advantages
 - Compliance should not be an issue with dialysis patients, as thrice-weekly dosing coincides with dialysis treatments
 - Increases likelihood of non-nephrologists prescribing roxadustat for non dialysis indications (on pharmacy benefit, no need to stock); may not be part of the bundle as oral drugs without IV equivalent are currently excluded from bundle
 - Reduces LDL and total cholesterol; does not raise (and may reduce) blood pressure (unlike ESAs)
- Potential questions on roxadustat:
 - HIF stabilization upregulates VEGF, which could potentially enhance tumor growth
 - However, this has not been seen either clinically or pre-clinically and several mechanisms suggest that HIF1 α could have tumor suppressive characteristics
 - In a Phase II trial of a FibroGen's previous HIF-PH inhibitor, FG-2216, a patient developed fatal hepatic necrosis and other patients had abnormal liver enzyme tests. As a result, the FDA suspended the trial and development was discontinued.
 - Currently unclear whether the death was drug-related and no signals have been seen so far with roxadustat
 - Some physicians may be slow to adopt a new anemia agent following the market withdrawal of AFFY's Omontys (peganesertide) due to several cases of anaphylaxis

Prolyl hydroxylase (PH) inhibition prevents the hydroxylation of HIF α , leading to upregulation of erythropoietin

(i) Normal conditions (normoxia) -- HIF is degraded

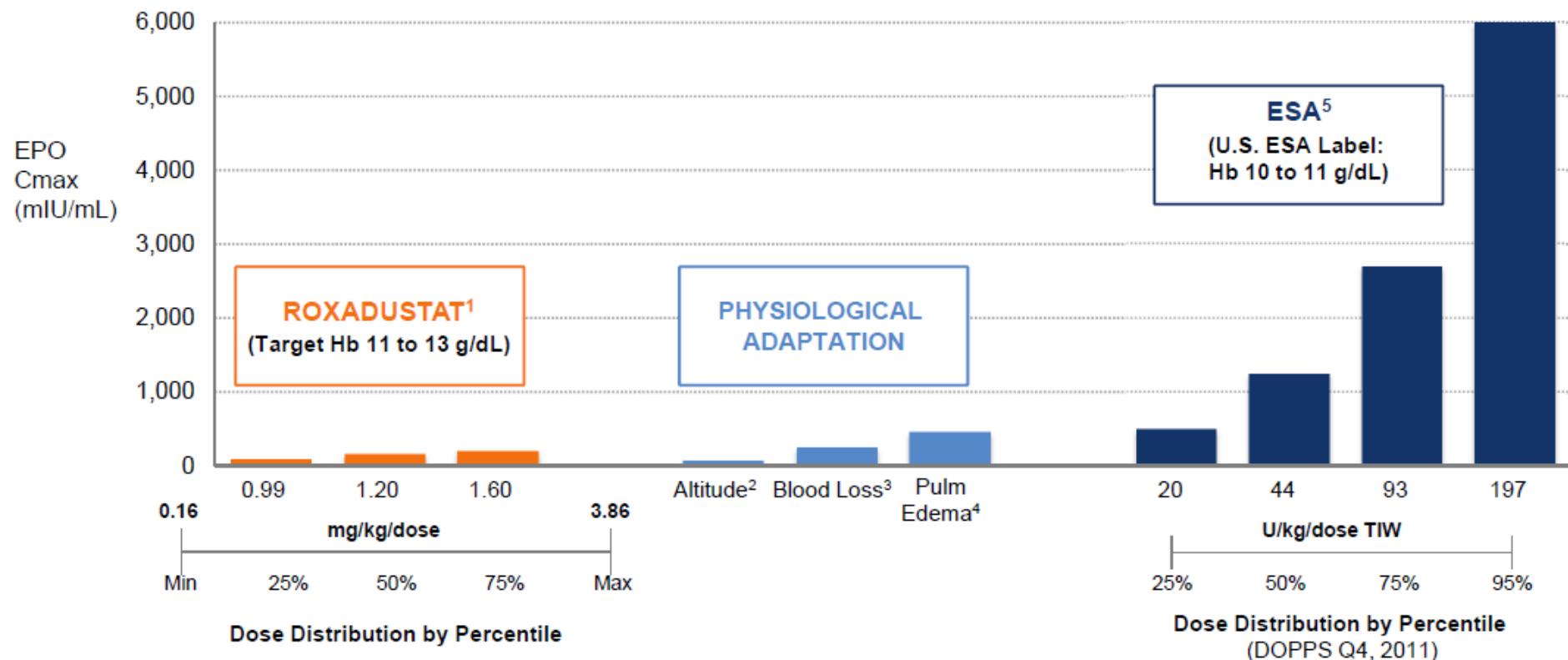


(ii) Hypoxic conditions / inhibition of proxyl hydroxylase -- HIF is stabilized



- Use of a PHD inhibitor mimics the effects of hypoxic conditions observed at high altitudes.
- There are three identified PHDs:
 - PHD2 plays a major role in the regulation of erythropoiesis by HIF, while PHD1 and PHD3 appear to be less important.
 - PHD1 has been implicated in ischemic tissue injury.
 - PHD3 appears to affect insulin signaling
- FGEN is also exploring the potential for PHD1 and PHD3-specific inhibitors for the protection of organs from ischemic damage and for the treatment of diabetes, respectively.

Roxadustat raises hemoglobin without increasing EPO concentrations to supraphysiological doses



¹ Cmax data for roxadustat estimated for a subset of 243 patients who achieved Hb response and were dosed at expected therapeutic doses.

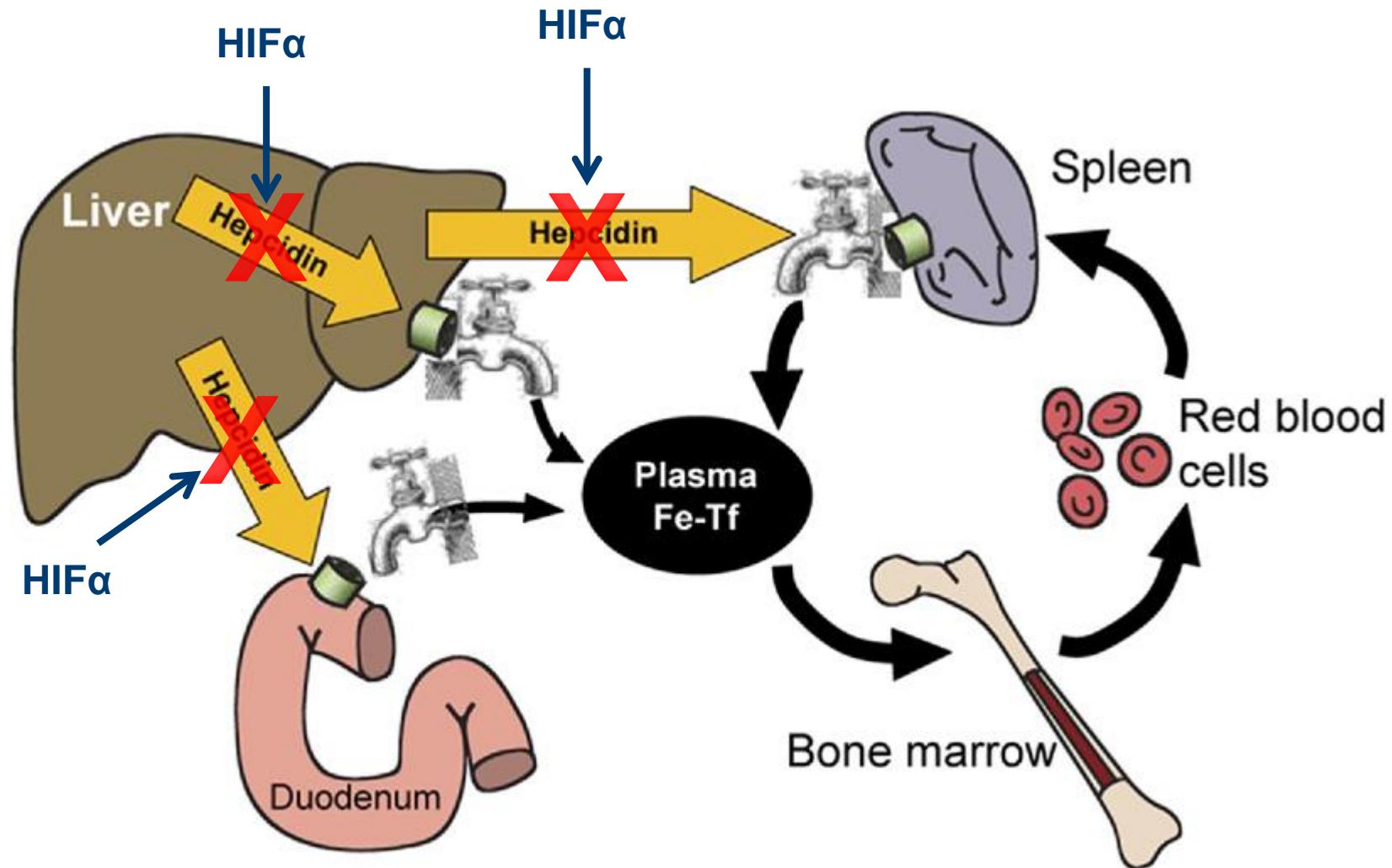
² Milledge & Cotes (1985) J Appl Physiol 59:360.

³ Goldberg et al. (1993), Clin Biochem 26:183, Maeda et al. (1992) Int J Hematol 55:111.

⁴ Kato et al. (1994) Ren Fail 16:645.

⁵ Based on Flaherty et al. (1990) Clin Pharmacol Ther 47:557.

HIF suppresses hepcidin, enhancing intestinal iron uptake and release from internal stores.

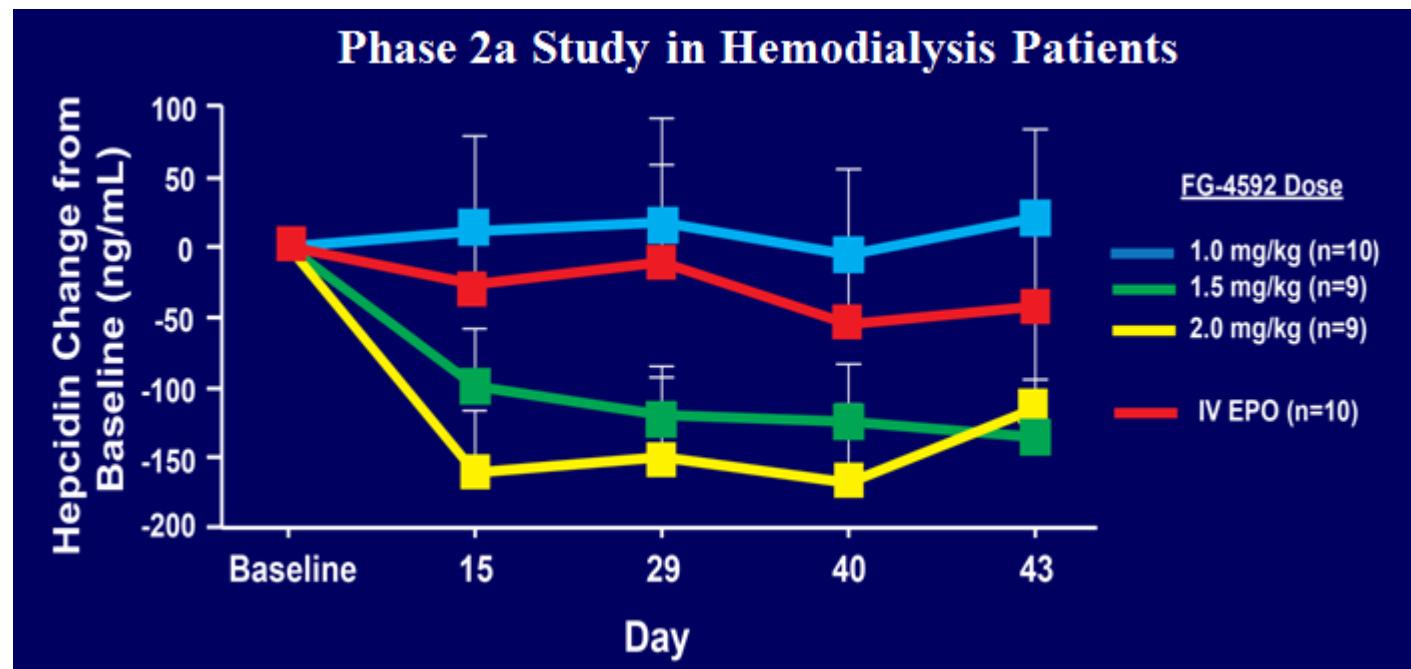


Roxadustat increases the bioavailability of oral iron and reduces the need for iron overall.

Fe-Tf = plasma iron bound to transferrin

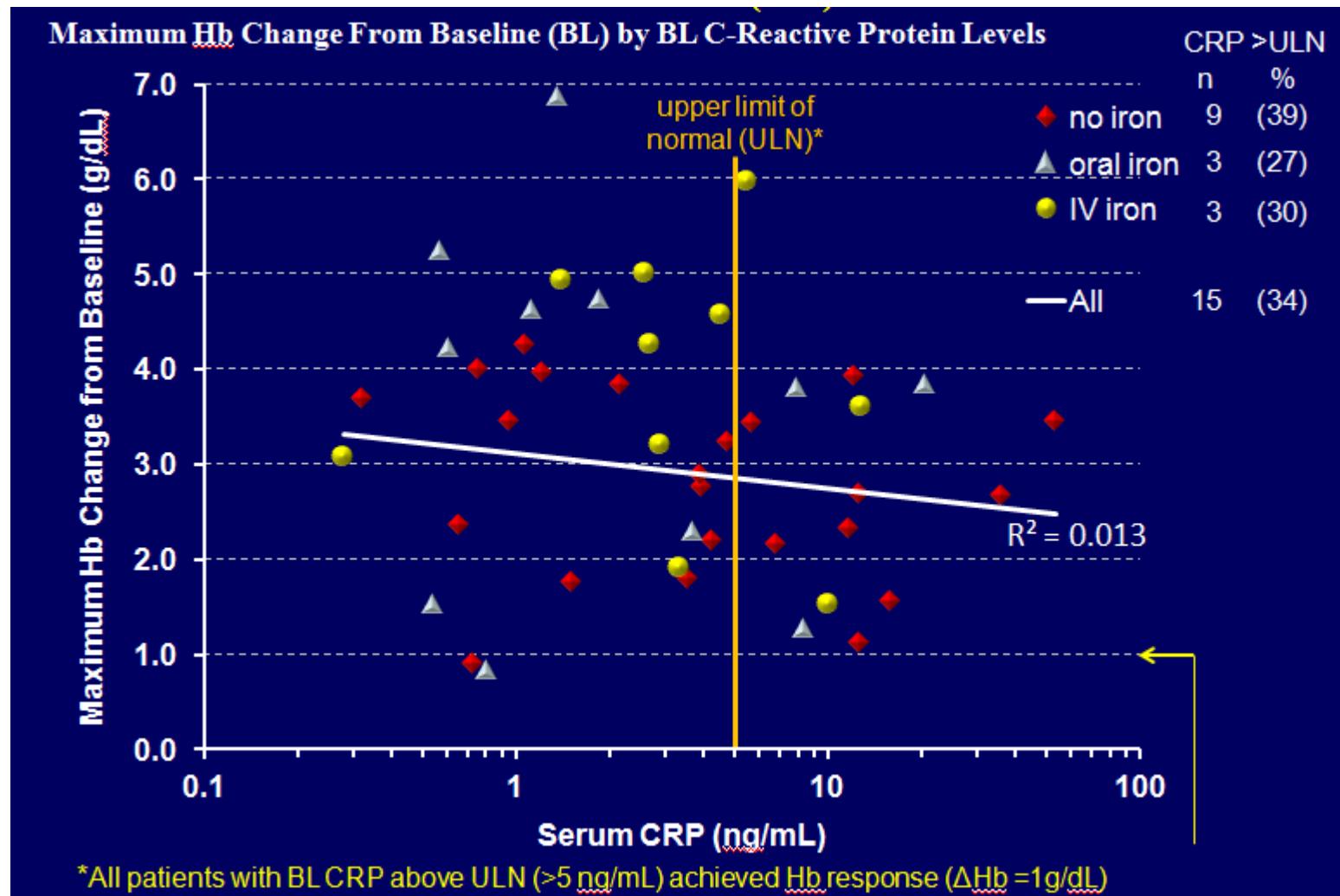
Source: Macdougall et al. 2012, Am J Kidney Dis. 59(3):444-451.

Roxadustat (FG-4592) lowers hepcidin levels in a dose-dependent manner



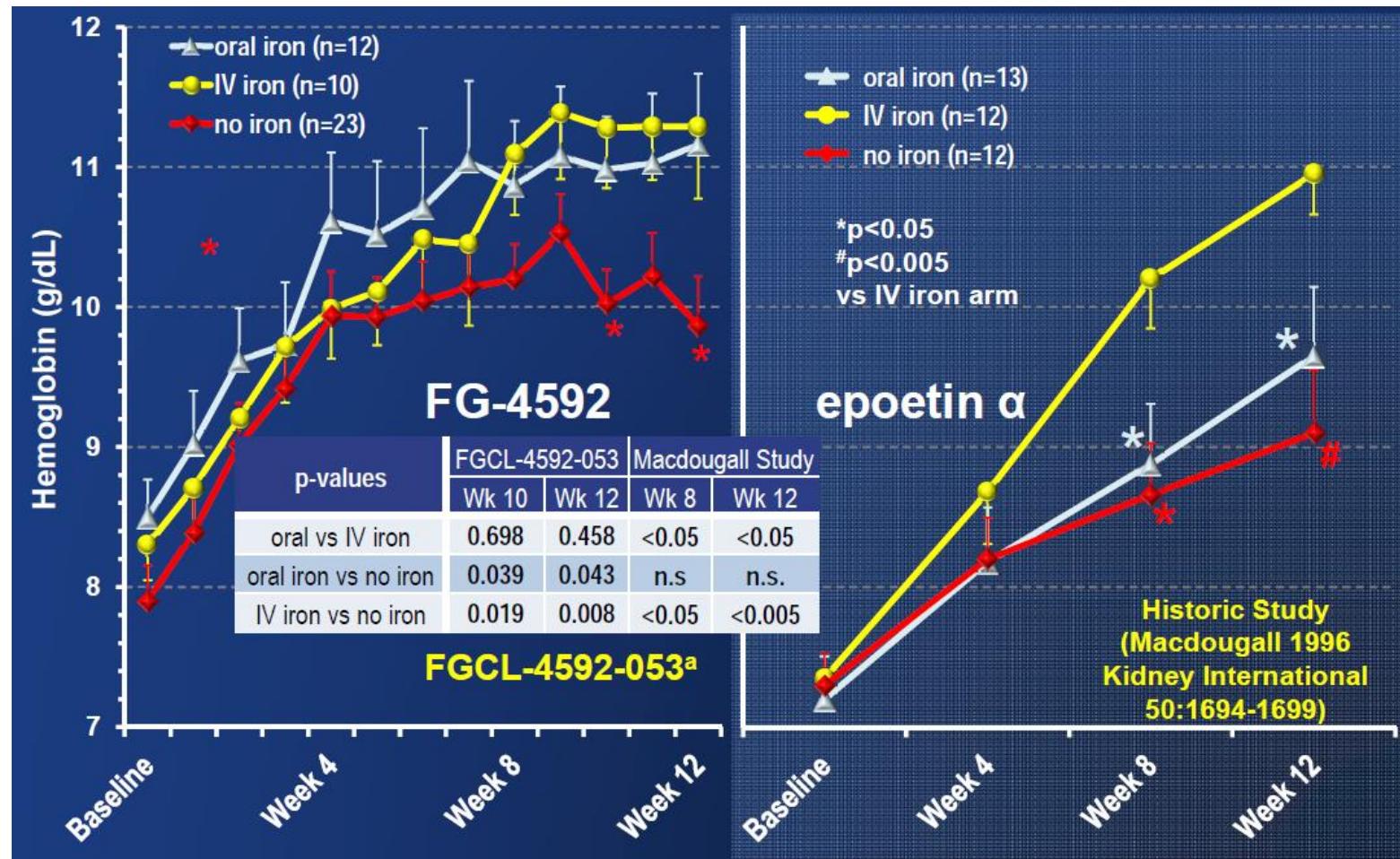
- Hepcidin is a peptide hormone made in the liver and the principal regulator of systemic iron homeostasis.
- Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal iron absorption, iron recycling by macrophages, and iron mobilization from hepatic stores.
- Elevated levels of hepcidin are believed to lead to iron deficiency.
- Hepcidin is elevated during infections and inflammation, causing a decrease in serum iron levels and contributing to the development of anemia of inflammation.
- Suppression of hepcidin by roxadustat may allow treatment of anemia in patients with inflammation who are hyporesponders to ESA

Hemoglobin (Hb) response to roxadustat is independent of baseline levels of C-reactive protein (CRP), a marker of inflammation



- This suggests that roxadustat is able to treat anemia in patients with inflammation who tend to hyporesponders to ESAs

Similar hemoglobin levels are achieved using either oral or IV iron in combination with roxadustat



- In Study 053, hemodialysis patients were randomized to receive roxadustat plus oral iron, IV iron, or no iron for 12 weeks.
- Both oral or IV iron administered with roxadustat maintained stable serum ferritin and transferrin saturation (TSAT).

Without IV iron, hemoglobin (Hb) increase with roxadustat is similar to Aranesp and EPO with IV iron in incident dialysis patients

Studies	FG-4592: FGCL-4592-053*			Darbepoetin: Study 211 ^b	
	No Iron	Oral Iron	IV Iron	Darbe-poetin	epoetina
Sample size	24	12	12	91	31
Treatment duration	12 weeks			20 weeks	
Baseline ferritin (mg/dL)	154	163	173	353	557
Baseline TSAT (%)	18	19	21	data not reported	
% patients who used IV iron	0	0	100%	92%	81%
Baseline Hb (g/dL)	7.9	8.5	8.3	8.6	8.5
Mean max Hb change (g/dL)	2.8	3.5	3.8	2.9	3.5

*Hemodialysis patient set only

a de Francisco et al. 2003. J Am Soc Nephrol 14:27A–28A (Abstract SA-FC124)

b Darbepoetin Study 211: FDA summary basis of approval

- Incident dialysis patients have the highest levels of mortality of all dialysis patients. The incident dialysis period is also the period during which mean ESA doses are generally highest.
- As increased mortality are associated with high ESA doses, roxadustat may offer a benefit to incident dialysis patients.
- The median roxadustat dose in Study 053 involving incident dialysis patients was 1.3 mg/kg; the endogenous EPO levels are comparable to the physiologic range naturally experienced by people adapting to high altitude or following blood donation.

Early data suggest a favorable safety profile of roxadustat in incident dialysis patients

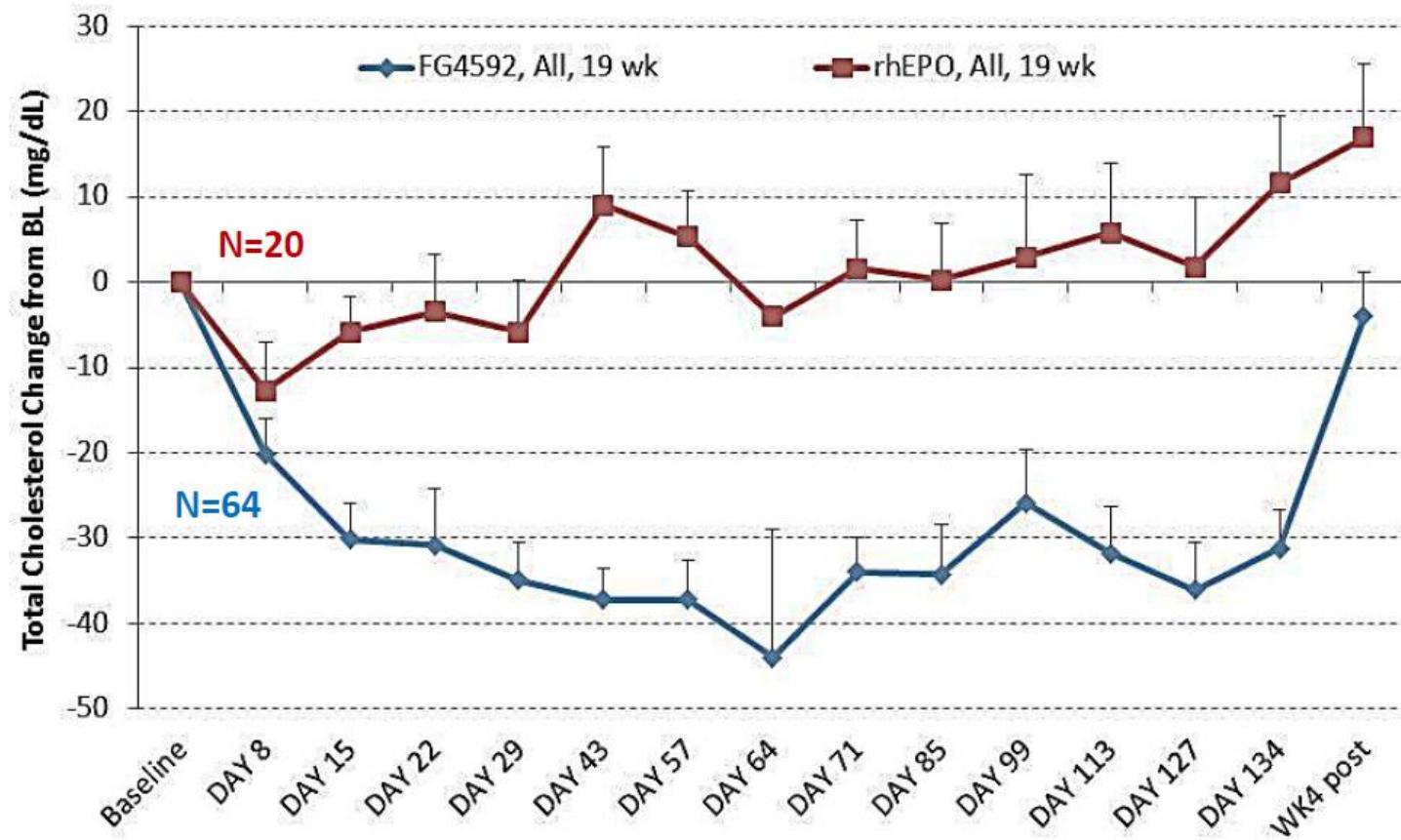
Studies	FG-4592: FGCL-4592-053*	Darbepoetin Study 211 ^b	
		Darbepoetin	Epoetin α
Sample size	48	91	31
Treatment duration	12 weeks	20 weeks	
# (%) hypertension AEs	4 (8.3%)	28 (31%)	14 (45%)
# (%) patients with SAE	4 (8.3%)	37 (41%)	11 (35%)
Deaths	1 (2.1%)	5 (6%)	1 (3%)

*Hemodialysis patient set only

a de Francisco et al. 2003. J Am Soc Nephrol 14:27A–28A (Abstract SA-FC124)

b Darbepoetin Study 211: FDA summary basis of approval

Roxadustat (FG4592) reduces total cholesterol levels compared to ESA



- In Phase II Study 040 involving dialysis patients, mean TC baseline (mg/dL):
 - Roxadustat (FG-4592) = 173.9 ± 5.6
 - Epoxy (rhEPO) = 166.7 ± 9.8

Non-Dialysis Patients – Phase II Study 041 – Roxadustat increases hemoglobin in patients with Stage 3 or 4 CKD

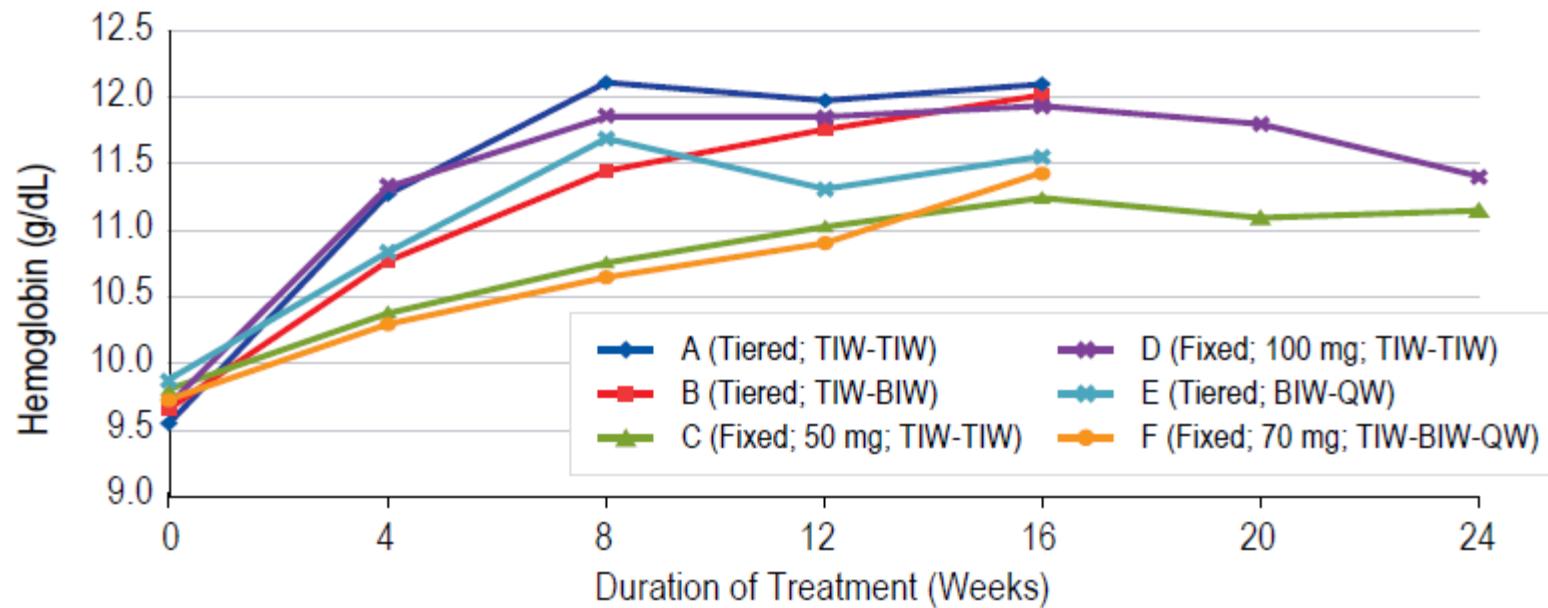


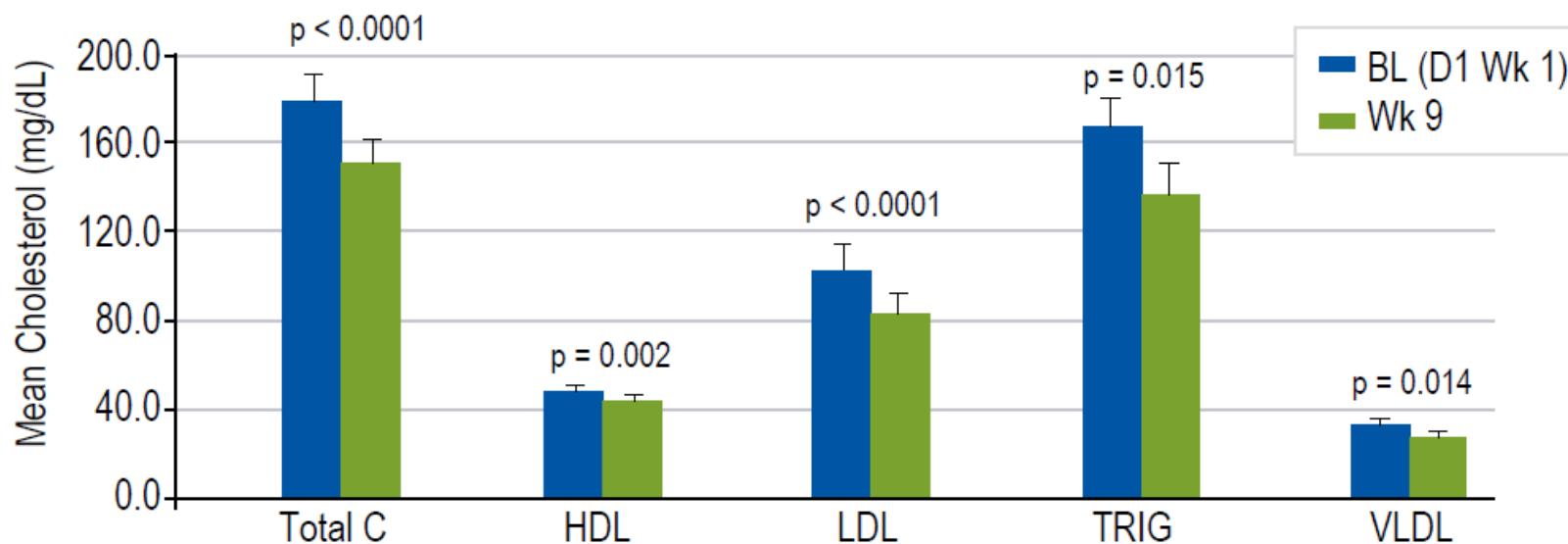
Table 1. Phase 2 FG-4592 Dosing Schedule

Cohort ^a	Treatment Duration (weeks)	FG-4592 Starting Dose (mg)			Correction and Maintenance Dosing
		Low Weight (40-60 kg)	Medium Weight (> 60-90 kg)	Heavy Weight (> 90-140 kg)	
A	16	60	100	140	TIW-TIW
B	16	60	100	140	TIW-BIW
C	24	-	50	-	TIW-TIW
D	24	-	100	-	TIW-TIW
E	24	70	100	150	BIW-QW
F	24	-	70	-	TIW-BIW-QW

Abbreviations: TIW = thrice weekly; BIW = twice weekly; QW = once weekly; kg = kilogram(s); mg = milligram(s); N = number of patients. ^aFor Cohorts A-E, N = 24; for Cohort F, N = 25.

Roxadustat lowers total and LDL cholesterol relative to baseline (Phase II Study 041 in non-Dialysis Patients)

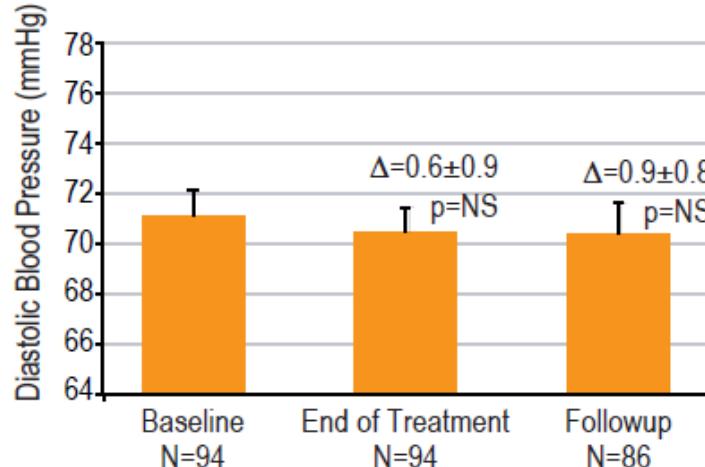
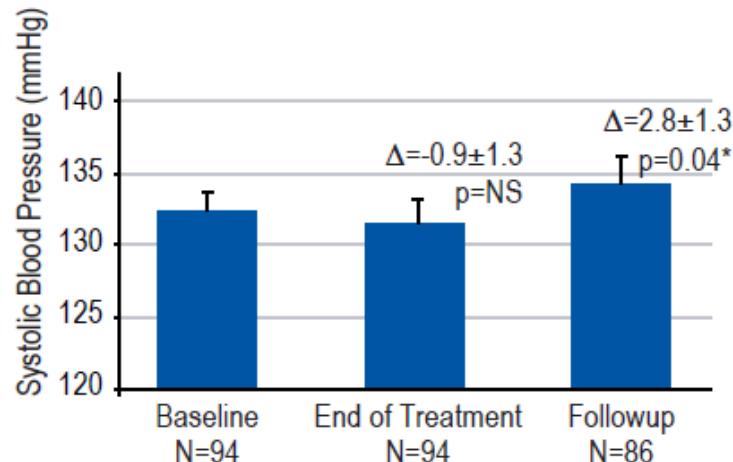
Figure 7. Mean (\pm SE) Changes in Lipids from Baseline to Week 9 (n=28)



Abbreviations: BL = baseline; C = cholesterol; D1W1 = Day 1 Week 1; dL = deciliter(s); mg = milligram(s); SE = standard error of the mean; Wk = Week.
p-values from Signed Rank Test.

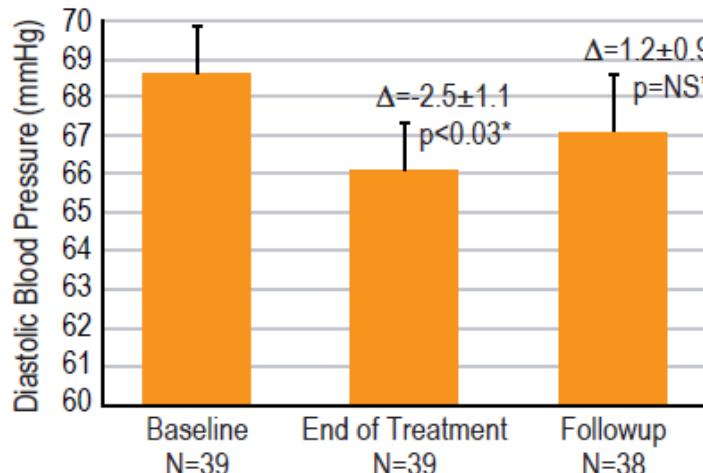
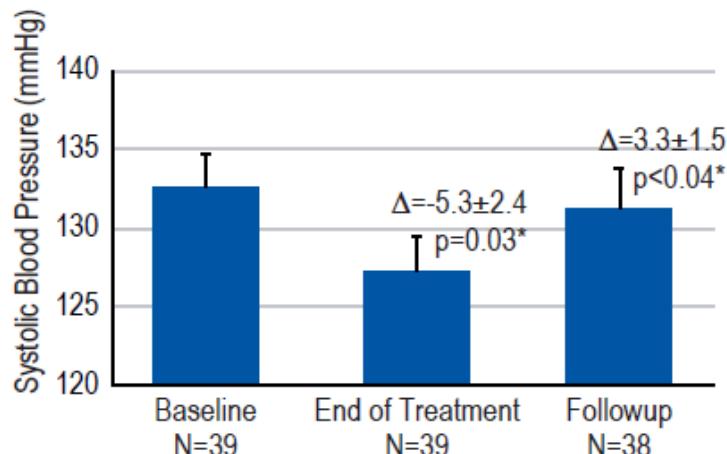
Non-Dialysis Patients – Phase II Study 041 – Roxadustat maintains or improves blood pressure relative to baseline

Roxadustat (TIW or BIW) does not increase blood pressure



*paired t-test

Roxadustat (TIW) reduces blood pressure



*paired t-test

Source: Besarab et al., ERA-EDTA 2012.

Summary of potential advantages of roxadustat over ESAs

Roxadustat	ESAs
Orally administered	Injected
Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI)	Recombinant erythropoietin (EPO)
Transiently and reversibly stabilizes HIF transcription factor with each dose	Binds EPO receptor
Mimics body's natural response to hypoxia	Exogenous hormone
Transient moderate increases in endogenous EPO level within physiologic range	Supraphysiological levels of exogenous EPO, risks off-target effects associated with ESAs
Suppresses serum hepcidin and promotes iron bioavailability via multiple pathways	Causes iron depletion/deficiency
Reduces cholesterol	No effect on cholesterol
Well tolerated in 1,271 subjects exposed to roxadustat in Phase I/II; no drug-related serious adverse events and no increase in thrombosis or hypertension	Safety concerns: increased risk of death, cardiovascular disease, hypertension, thrombosis, stroke

Summary of KOL feedback

- In general, the MEDACorp nephrology key opinion leaders (KOLs) to whom we spoke were excited about the potential for roxadustat, noting the potential of a wholesale shift from the current standard of care if the drug is shown to improve cardiovascular outcomes relative to ESAs,. One nephrologist noted that a 5-10% improvement in MACE events, even if not statistically significant, could be clinically meaningful enough to drive adoption of the agent. On the other hand, he suggested that if the rates of events appeared worse in the roxadustat arm (vs. EpoGen), it would be a tough sell even if it is statistically non-inferior.
- Regarding the reasons for the CV toxicity associated with higher Hb levels during ESA administration, while there is no definitive proof, KOLs generally believe it is most likely related to the dose of the drug rather than the Hb level achieved.
- If approved, the KOLs noted that uptake of roxadustat in the dialysis setting will likely be dependent on both the reimbursement (i.e., will it be included in the bundle) and contracting with large dialysis providers (~2/3 of all dialysis centers in the US are owned by DaVita and Fresenius).
- In the non-dialysis CKD market, the KOLs believe that a safe, oral agent could also find meaningful uptake as well as expand the market. One noted that use of ESAs in these patients was relatively low even before publication of the CHOIR and CREATE trial due to the route of administration.
- While the interviewed nephrologists recognized the theoretical potential for tumorigenesis or increased tumor growth due to the increased expression of VEGF or other HIF-related genes, most did not seem overly concerned. Specialists in the PHD/HIF pathway space suggested that the risk is low given that most patients with germ-line PHD inactivating mutations do not have an increased risk of cancer (unlike patients with other mutations in the same pathway).

Key Investment Considerations --

**Preponderance of Data Suggest
That High EPO Levels, Rather
Than Increased Hb Are
Responsible for CV Toxicities**

Several explanations for the increased CV events associated with ESAs

1) The increase in Hb (regardless of ESA dose) is the proximate cause of increased CV risk.

- This could occur through increased blood volume or viscosity, or through other pathways
- However, most evidence to date indicates that elevation of Hb into the normal range occurring spontaneously is not pathogenic, but is associated with reduced rates of cardiovascular events.

2) ESA resistance reflects a state of advanced illness, which confounds the relationship between CV outcomes and ESA administration.

- ESA resistance has been associated with generalized illness, androgen deficiency, infection and inflammation, increased cytokine signaling, secondary hyperparathyroidism, use of drugs that antagonize the renin-angiotensin system, and acquired defects in iron transport.
- However, there are no plausible explanations of how resistance to ESA could cause or promote atherosclerosis, myocardial disease, or other forms of CV disease.

3) ESA therapy has a dose- or exposure-related CV toxicity

- Biologic explanations for ESAs causing or worsening CV disease include increased sensitivity of α -adrenergic receptors, elevations in blood pressure, and increased thrombo-genicity with supra-physiologic exposure to the drug.

The third explanation appears to be the most commonly favored, per our discussions with KOLs, and is supported by several analyses...

In a subset analysis of the CHOIR trial, CV risks appear to be associated with higher ESA doses regardless of Hb achieved

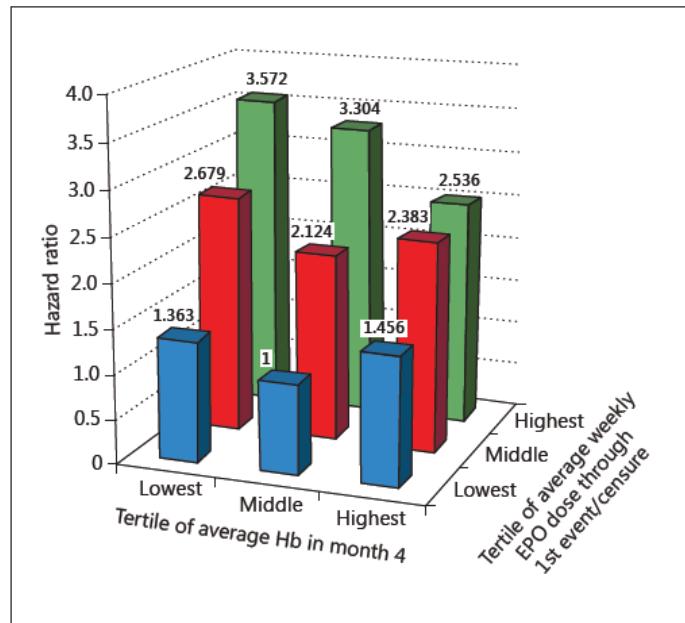


Fig. 1. Cox proportional hazards for the primary composite end point of death, heart failure hospitalization, stroke, or myocardial infarction, according to the tertile of Hb achieved at 4 months and the long-term maintenance epoetin-alfa (EPO) dose received. The middle tertile is set as referent. The x-axis represents average Hb in month 4, and the y-axis represents the average weekly dose of EPO received prior to the first event or time of censure. Average Hb tertiles were (g/dl): lowest ≤ 11.5 , middle > 11.5 to < 12.7 , highest ≥ 12.7 . Average weekly EPO dose tertiles prior to first event were (1,000 units): lowest $< 5,164$, middle $5,164-10,095$, highest $> 10,095$.

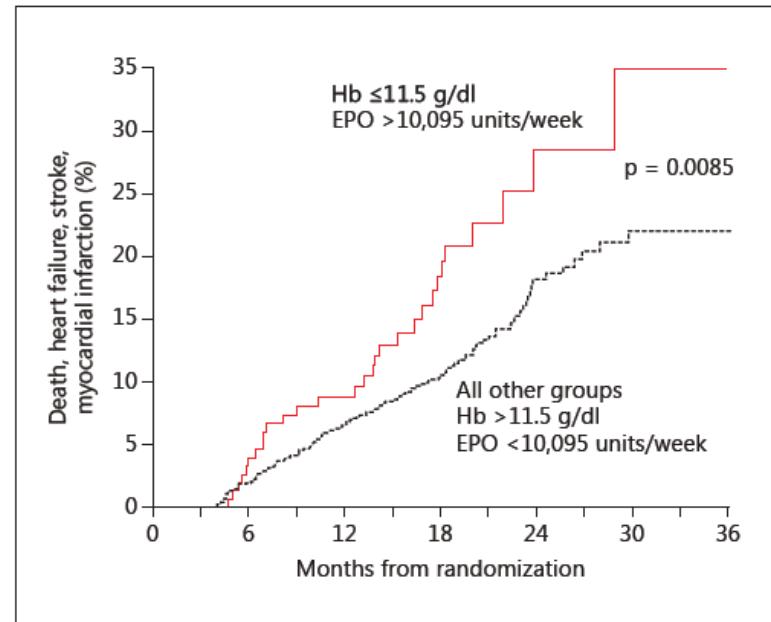
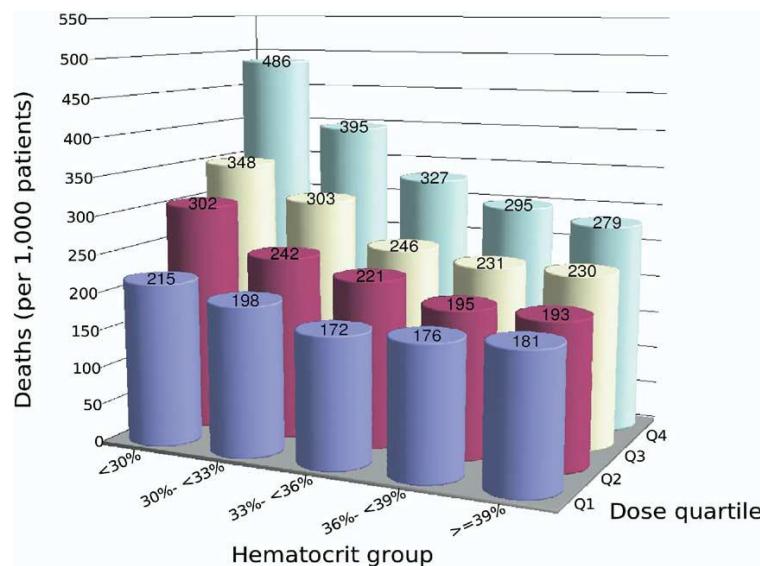


Fig. 2. Kaplan-Meier survival curves for the lowest tertile of the average Hb achieved in month 4 for patients ($n = 1,224$) who went on to receive the highest average weekly epoetin-alfa (EPO) dose up to the time of the first event or censure ($Hb \leq 11.5$ g/dl with $EPO > 10,095$ units/week) compared to the remaining 8 tertiles by tertile groups ($Hb > 11.5$ g/dl with $EPO < 10,095$ units/week), log-rank p value = 0.0085.

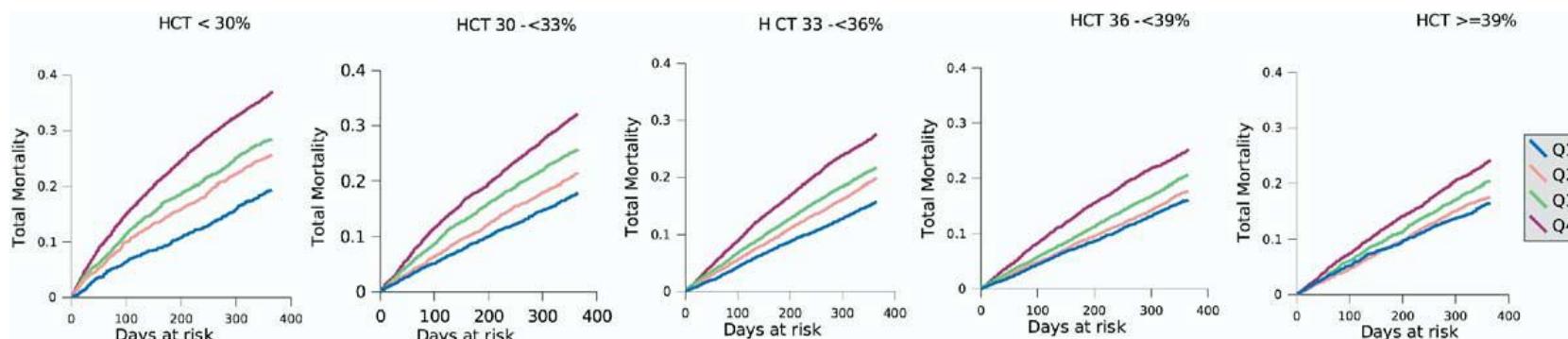
- In non-dialysis CKD patients, average Epogen doses $> 10,095$ units/week were associated with increased risks for CV events irrespective of the Hb achieved within the first 4 months of treatment.

An analysis of USRDS data shows that higher ESA dose is associated with increased mortality even after controlling for hematocrit levels



Unadjusted 1-year mortality rates by hematocrit group according to epoetin dose quartile.

- Using data from 94,569 hemodialysis patients in the US Renal Data System (USRDS) from 2000-2001, Zhang et al. (2004), found increasing mortality by ESA dose quartile among patients with similar hematocrit scores.
- Hematocrit is the percentage of whole blood volume that consists of red blood cells.
 - The percentage is ~3x the hemoglobin (as measured in g/dL)
 - Normal range is ~41-50% for males and ~36-44% for females
- However, it is not clear from these data whether the higher ESA dose is causing the increased mortality or whether those patients requiring higher ESA doses to achieve similar hematocrit levels (hyporesponders) have a worse prognosis for other reasons.



Cumulative mortality rates by epoetin dose quartiles according to hematocrit group.

In a meta-analysis, ESA dose was associated with increased all-cause mortality, even after adjusting for achieved Hb level

Table 2. Metaregression Analyses of the Association of ESA Dose With All-Cause and Cardiovascular Mortality

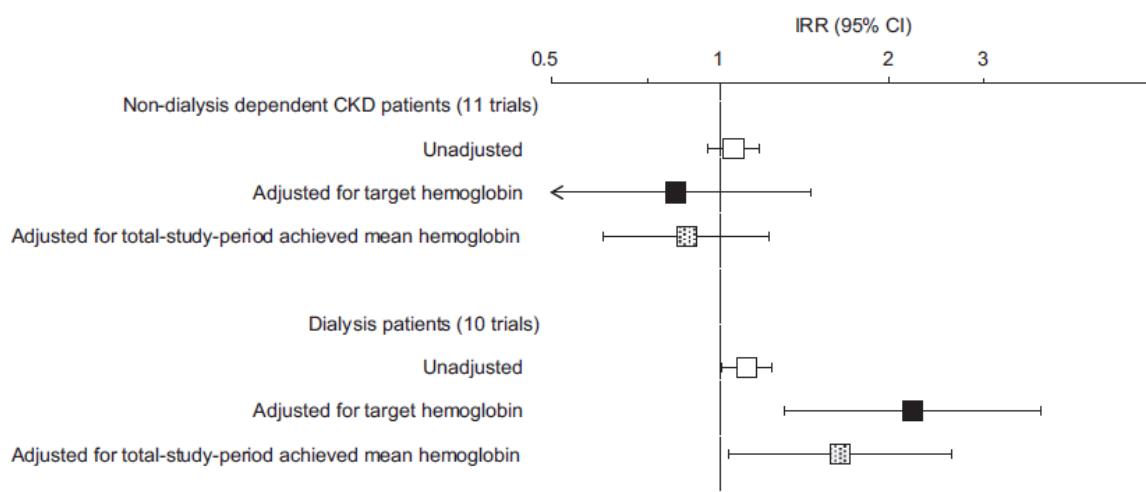
Outcome/Predictor	No. of Patients	No. of Trials	IRR (95% CI)	P
All-cause mortality				
First-3-mo mean ESA dose				
Unadjusted	4,565	11	1.42 (1.10-1.83)	0.007
Adjusted for target Hb	4,385	10	1.71 (0.90-3.24)	0.1
Adjusted for first-3-mo achieved mean Hb	4,565	11	1.48 (1.02-2.14)	0.04
Total-study-period mean ESA dose				
Unadjusted	11,285	21	1.09 (1.02-1.18)	0.02
Adjusted for target Hb	11,105	21	1.41 (1.08-1.82)	0.01
Adjusted for total-study-period achieved mean Hb	11,285	21	1.27 (0.97-1.65)	0.08
Cardiovascular mortality				
First-3-mo mean ESA dose				
Unadjusted	2,085	6	1.31 (0.92-1.86)	0.1
Adjusted for target Hb	1,979	5	Not performed ^a	—
Adjusted for first-3-mo achieved mean Hb	2,085	6	Not performed ^a	—
Total-study-period mean ESA dose				
Unadjusted	7,148	10	1.07 (0.97-1.17)	0.2
Adjusted for target Hb	7,042	10	Not performed ^b	—
Adjusted for total-study-period achieved mean Hb	7,148	10	1.38 (0.93-2.03)	0.1

Note: ESA dose is per epoetin alfa-equivalent 10,000-U/wk increment.

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IRR, incidence rate ratio.

^aThe analysis was not performed due to insufficient observations.

^bThe analysis was not performed due to collinearity.



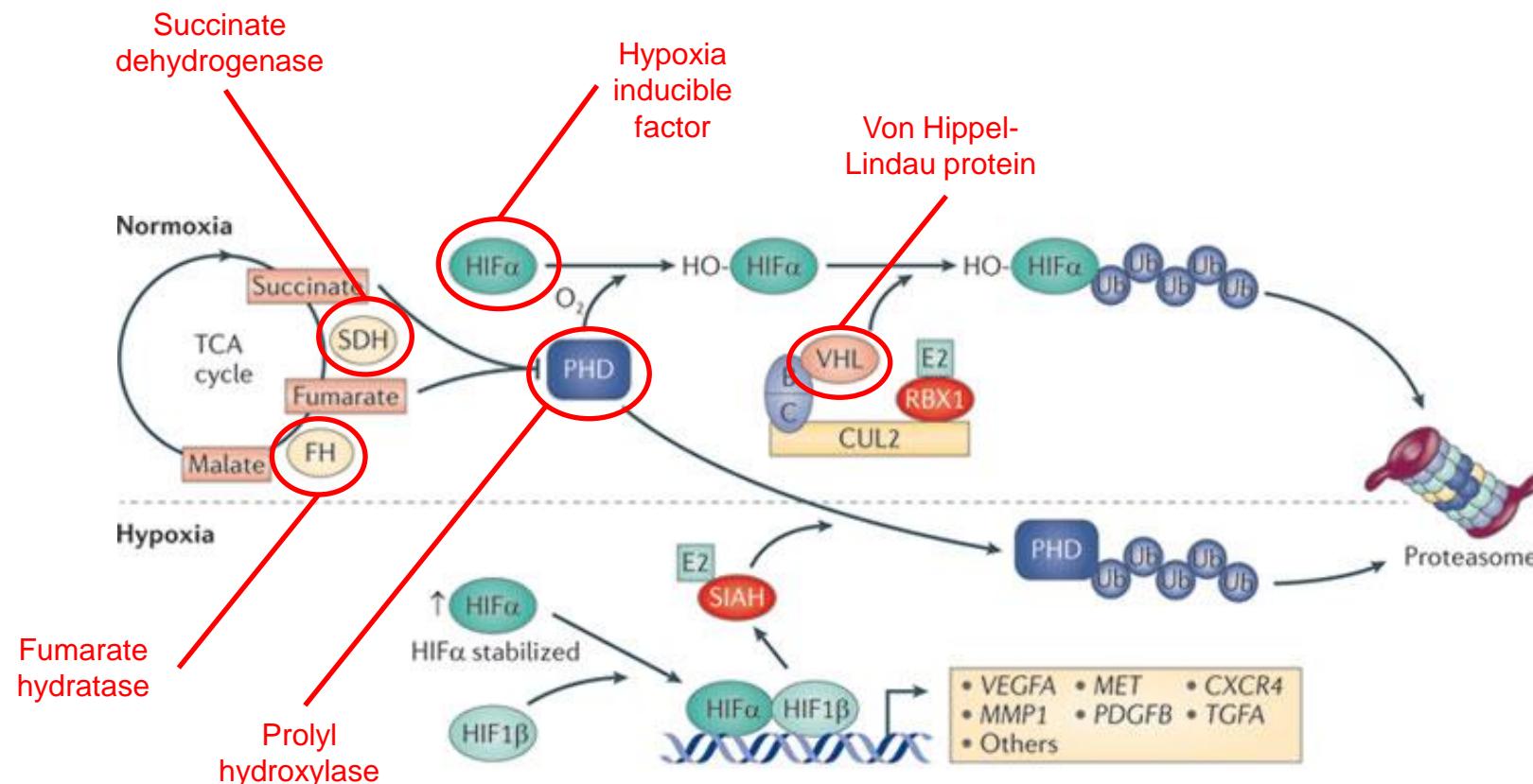
Source: Koulouridis et al., AJKD (2012)

- This metaregression analysis (Koulouridis et al., 2012) included 31 trials and 12,956 dialysis and non-dialysis ESA-treated CKD patients.
- Higher mean ESA dose (for both the first 3 months and total study period) was associated with higher all-cause mortality.
- These associations remained significant after adjusting for achieved mean Hb (for both the first 3 months and total period) and for target Hb (total period only)
- Similar all-cause mortality associations were seen when restricted to dialysis patients only
- While not significant, there appeared to be a trend towards a similar relationship for CV mortality in the overall meta-analysis population.

Key Investment Considerations --

**Could There Be Cancer and CV
Risks Associated with HIF
Stabilization?**

Several germ-line mutations in the PHD2-HIF-VHL pathway have been shown to stabilize HIF in the absence of hypoxia



- Mutations in prolyl hydroxylase (PHD) and HIF can result in a “pseudo-hypoxic” state, causing constitutive activation of HIF, and upregulating many genes, including those involved in angiogenesis, erythropoiesis, and cell metabolism, proliferation, and survival. For example, upregulation of VEGF can potentially enhance tumor growth and proliferative diabetic retinopathy.
- The Von Hippel-Lindau (VHL) protein acts downstream of PHD to aid in the degradation of HIF. Mutations in the gene for this protein can also result in HIF stabilization.
- Mutations in succinate dehydrogenase (SDH) and fumarate hydratase (FH), two enzymes in the tricarboxylic acid (TCA) cycle, can lead to accumulation of fumarate and succinate, which have been shown to be inhibitors of PHD.
- Individuals with some of these mutations are predisposed to certain cancer (discussed on the next slide). Inhibition of PHD by roxadustat has not been associated with tumorigenesis or growth of existing tumors to date, but safety data from longer term trials will be important to assess.

Mixed reports on the association of cancer risks with mutations in the PHD2-HIF- VHL pathway – overall risks considered low by MEDACorp KOLs

- Germ-line mutations in VHL

- Von Hippel-Lindau disease
 - Patients are predisposed to multiple vascularized tumors, including hemangioblastomas of the central nervous system and retina, clear-cell renal-cell carcinomas, pheochromocytomas, endocrine pancreatic tumors, and endolymphatic sac tumors.
- Chuvash congenital polycythemia
 - A homozygous 598C→T (R200W) germ-line mutation of VHL was first reported in residents of the Chuvash Autonomous Republic of the Russian Federation. These patients have increased erythropoietin production, but are not predisposed to cancer.

- Germ-line mutations in PHD2 and HIF-2α

- Heterozygous germ-line mutations in the PHD2 and HIF-2α genes can lead to erythrocytosis and increased erythropoietin level, but these do not appear to predispose patients to cancer.
 - However, one case report (Ladroue et al, 2008) identified a patient with a PHD2 mutation (H374R) who developed recurrent paraganglioma at age 43. A loss-of-heterozygosity (LOH) of PHD2 was confirmed in the tumor.
 - The authors noted that other patients with heterozygous germ-line PHD2 mutations who have been described in literature were younger than this patient, with the exception of a 54-year old with hypertension, which may have been caused by catecholamine secretion from a misdiagnosed paraganglioma.

- Germ-line mutations in FH and SDH

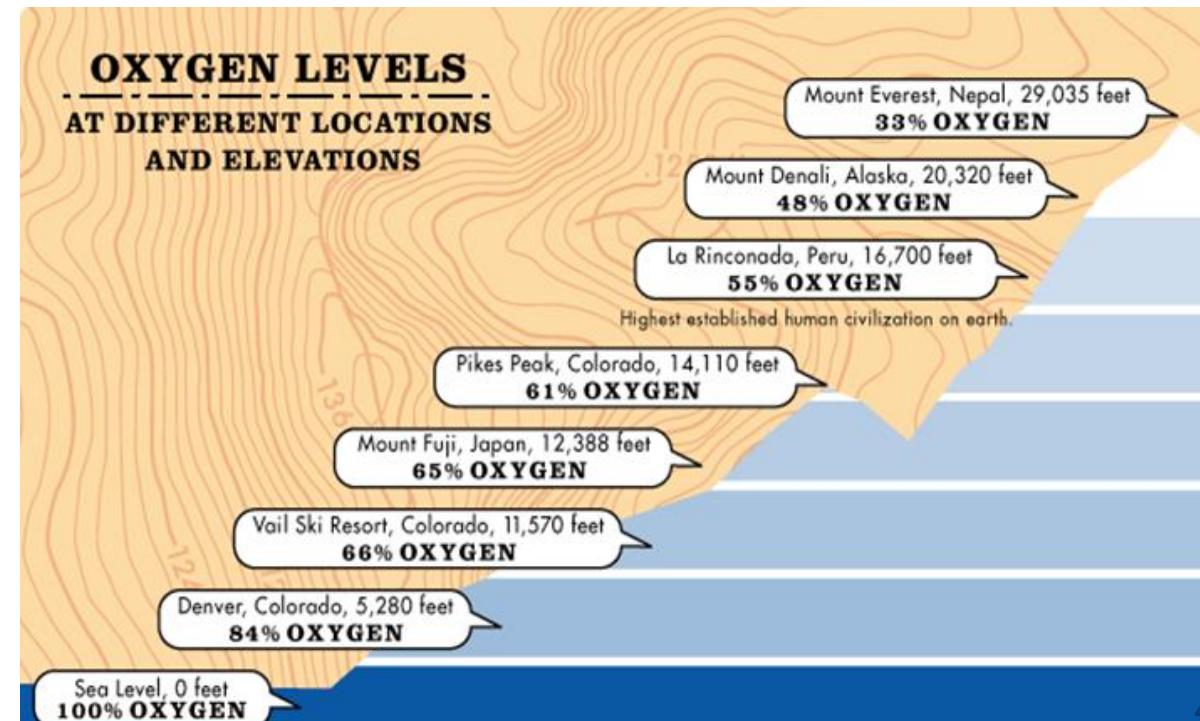
- These two mitochondrial enzymes have been implicated in the development of the hereditary leiomyomatosis and renal-cell cancer syndrome and the hereditary paraganglioma–pheochromocytoma syndrome.

Preclinical models suggest HIF and PHD can act as either tumor promoters or suppressors

- There is some biological rationale that HIF can act as a tumor promoter:
 - HIF can induce autocrine and paracrine cancer cell growth factors (TGF α and PDGF B), promote invasion (through MMP and LOX) and promote angiogenesis (through VEGF).
 - Deletions in HIF α have been shown to decrease tumor growth in nude mouse subcutaneous xenograft assays.
- While other evidence suggests that it can also act as a tumor suppressor:
 - Deletion of HIF1 α promotes growth of teratocarcinomas and orthotopic tumors preclinical.
 - Deletion of HIF2 α has been shown to promote growth of K-Ras-driven lung adenocarcinomas in genetically engineered mice and the growth of astrocytomas.
- According to Kaelin (2011), preclinical evidence appears to suggest that **HIF2 α may be a kidney cancer oncoprotein** whereas **HIF1 α may act as a kidney cancer tumor suppressor**:
 - VHL protein-defective kidney cancers can produce high levels of both HIF1 α and HIF2 α (or HIF2 α only).
 - In preclinical models, elimination of HIF2 α is sufficient to inhibit tumor growth.
 - Restoration HIF2 α has been shown to be sufficient to override suppression by VHL protein.
 - However, Schietke et al. (2012) showed that HIF2 α expression in renal epithelial cells requires VHL inactivation, suggesting that PHD inhibition alone may not be enough to cause renal cell carcinoma (RCC) provided functional VHL protein remains
 - Additionally, many VHL protein-deficient renal carcinoma lines harbor mutations that lead to missing or defective HIF1 α protein.
 - Restoration of wild-type HIF1 α suppresses the ability of these cells to proliferate in vitro and in vivo.
 - Elimination of HIF1 α in HIF1 α -proficient cells enhances their proliferation in vitro and in vivo.
- Kaelin also suggested that SDH mutations may lead to paragangliomas in a PHD-dependent, but HIF-independent, manner, suggesting that inhibition of PHD may affect tumorigensis or tumor growth through other pathways.
- Interestingly, Ameln et al. (2011) showed that inhibition of PHD2 caused a profound reduction in tumor growth in mice through the TGFB pathway, also in a HIF-independent manner.

HIF stabilization is involved in body's natural response to hypoxic conditions such as high altitude

- The hypoxia-inducible factor (HIF) pathway plays a protective role in regulating genes that mitigate the effects of low oxygen tension.
- Under normoxic conditions, oxygen-sensitive HIF-alpha isoforms are rendered inactive via proline hydroxylation by HIF-specific prolyl hydroxylases (HIF-PHs), which lead to binding of von Hippel–Lindau protein and targeted degradation through the ubiquitinproteasome pathway.
- Under hypoxic conditions (where less oxygen substrate is available for proline hydroxylation by HIF-PHs), HIF-alpha isoforms are stabilized, heterodimerize with HIF-beta, and translocate to the nucleus where they bind to hypoxia-responsive element motifs. In cooperation with other transcriptional coactivators, HIF induces transcription of genes that ameliorate the effects of hypoxia.
- HIF PH inhibitors (PHIs) such as roxadustat pharmacologically inhibit HIF-PHs, thereby preventing HIF-alpha degradation and leading to HIF-dependent transcription.
- Therefore studies of people living in high altitude may provide a proxy for the biological consequences of PH inhibition.



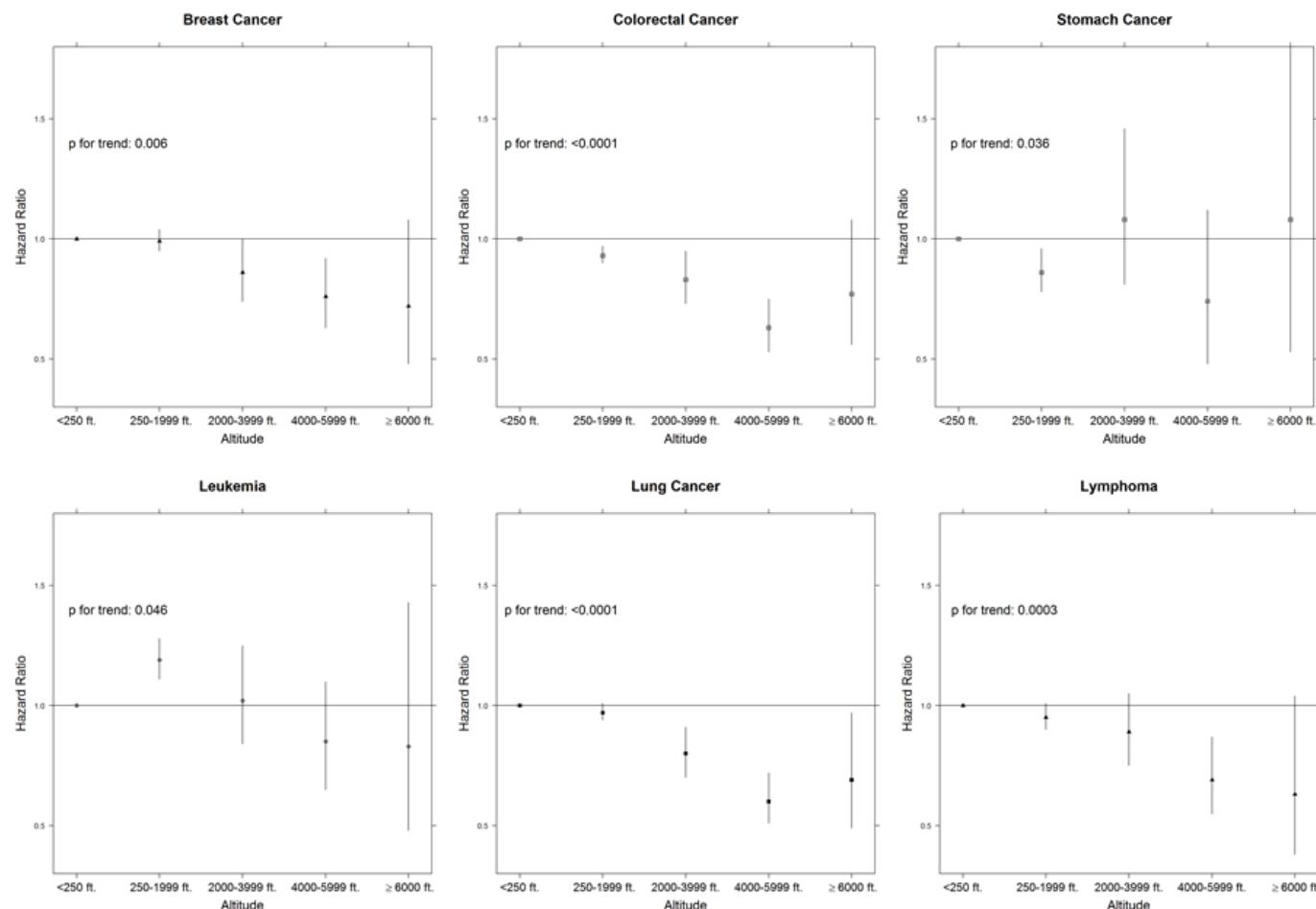
High altitude is associated with reduced cancer risks in patients with renal disease

- In a cohort of 928,965 dialysis patients from the USRDS (1995-2006) stratified by the elevation of their zip code, the incidence of six common tumor types appeared to decrease at higher altitudes, although the biological mechanism for this is unclear.

Events and event rate per 1,000 person years

	Events	Rate
Breast Cancer		
< 250 ft.	3,441	6.70
250-1999 ft.	4,533	6.65
2000-3999 ft.	187	5.20
4000-5999 ft.	110	4.37
≥ 6000 ft.	24	3.78
Colorectal Cancer		
< 250 ft.	4,446	3.97
250-1999 ft.	5,455	3.64
2000-3999 ft.	244	3.09
4000-5999 ft.	130	2.27
≥ 6000 ft.	37	2.69
Lung Cancer		
< 250 ft.	4,751	4.22
250-1999 ft.	6,310	4.20
2000-3999 ft.	257	3.24
4000-5999 ft.	133	2.33
≥ 6000 ft.	33	2.39
Stomach Cancer		
< 250 ft.	702	0.62
250-1999 ft.	775	0.51
2000-3999 ft.	48	0.61
4000-5999 ft.	23	0.40
≥ 6000 ft.	8	0.58
Lymphoma		
< 250 ft.	2,222	1.98
250-1999 ft.	2,871	1.91
2000-3999 ft.	144	1.82
4000-5999 ft.	77	1.35
≥ 6000 ft.	15	1.09
Leukemia		
< 250 ft.	1,361	1.21
250-1999 ft.	2,228	1.48
2000-3999 ft.	104	1.31
4000-5999 ft.	59	1.03
≥ 6000 ft.	13	0.94

Incidence rates of six cancers in U.S. dialysis patients across altitude strata



- Most other studies looking at cancer or overall mortality in the general population have found either no association or a beneficial effect for living at high altitudes.

There is a report of increased severity of paragangliomas for carriers of genetic mutations living at higher altitudes but its significance is unclear

- It has been recognized since the early 1970s that living at high altitudes can have an effect on the development of carotid body tumors. High-altitude paragangliomas can have a prevalence of up to 1 in 10 in humans and 1 in 2 in bovines (compared to a low-altitude prevalence of 1 in 500,000 or less). Since then, it has been suggested that SDH mutations in these tumors can play a role in creating a “pseudo-hypoxia”, potentially through the inhibition of PHD and/or subsequent stabilization of HIF.
- One study (Astrom 2003) found that among individuals with hereditary paragangliomas and SDHD mutations, there was a correlation between altitude and the phenotypic severity of the disease. Those individuals diagnosed with multiple tumors at their first clinical evaluation lived at higher average altitudes and were exposed to higher altitude-years than those diagnosed with one or no tumors (see below). Additionally, patients who developed pheochromocytomas also lived at higher average altitudes for longer periods of time than those who did not.
- This suggests that hypoxia at high altitudes could lead to increased tumorigenesis or altered phenotype for these rare cancers, at least in patients with existing pseudo-hypoxia induced by SDHD mutations. However, as noted above, it has been suggested that SDH mutations lead to paraganlioma in a PHD-dependent, but HIF-independent manner (Kaelin 2011). As such, it remains unclear what role HIF itself plays, and whether inhibition of PHD by roxadustat could have a similar effect.

Table 2 Tumor multiplicity versus altitude at the first diagnostic evaluation (mean ± SE)

	0–1 Tumor (n=26)	Multiple tumors (n=32)	All (n=58)	NP P-value ^a
Age at symptom onset [ASO] (years)	32.6±2.9 ^b	29.0±2.1	30.6±1.7 ^b	0.25
Age at clinical diagnosis [ACD] (years)	33.8±2.8	34.5±2.2	34.2±1.7	0.30
Altitude [h(ACD)] (m)	200.9±22.0	452.8±80.0	340.0±47.8	0.0487
Altitude-year [h(ACD)×ACD] (m × year)	6,564±922	15,625±2,774	11,585±1,682	0.0117
Missense/nonsense-splicing	16/10	17/15	33/25	0.35

^aNon-parametric (NP) tests, one-sided, comparing “0–1 Tumor” with “Multiple tumors”
^bExcluding one subject without tumor

Table 5 Altitude and pheochromocytoma and malignancy development in lifetime (mean ± SE)

	Pheochromocytoma (n=6)	No pheochromocytoma (n=51)	NP P-value ^a	Malignancy (n=4)	No malignancy (n=53)	NP P-value ^a
Current age (years)	47.8±3.5	52.0±2.2	0.27	44.9±1.83	52.1±2.1	0.17
Altitude [h(CA)] (m)	863.2±244.6	274.5±37.8	0.013	282.4±107.13	340.6±50.9	0.49
Altitude × year [h(CA)×CA]	42,472±12,220	13,151±1,704	0.026	12,554±4,765	16,515±2,422	0.46
Missense/nonsense-splicing	1/5 ^b	31/20	0.052	3/1	29/24	0.40

^aNon-parametric tests (NP), one-sided, comparing “Pheochromocytoma” and “No pheochromocytoma” groups, and “Malignancy” and “No malignancy” groups, respectively

^bMutations associated with pheochromocytomas include W43X (n=4), L128fsX134 and P81L

No cancer signal has been observed to date in clinical or preclinical roxadustat studies

- FGEN has conducted 12 tumor studies in rodents, including xenograft, syngeneic, or spontaneous tumors of lung, colon, breast, pancreas, melanoma, ovarian, renal, prostate and leukemic origin, and has found no effect of roxadustat on tumor promotion
 - Additionally, the company has conducted similar studies on five other HIF-PH inhibitors in similar models, for a total of 35 studies of six HIF-PH inhibitors in 18 models total, with no observed effects on tumor initiation, promotion, or metastases.
 - Several of these tumors models tested are reported to be dependent on VEGF; however no significant increases in plasma VEGF levels were seen in any of these preclinical studies using clinically relevant doses of roxadustat.
- Two-year rat and mouse carcinogenicity studies with roxadustat have been completed and there is nothing to report; according to management, one other HIF-PH inhibitor has also undergone carcinogenicity studies and was clean.
- No evidence suggesting tumor risk has been identified in clinical studies to date.
- Additionally, the once-, twice-, and thrice-weekly roxadustat dosing schedules being pursued by FGEN leads to intermittent PHD inhibition and stabilization of HIF. While it remains to be seen how this could affect the safety of the drug, we note that the cancer risk resulting from most of the aforementioned germ-line mutation patients and preclinical models may have resulted from the continuous effect of the mutated genes. Allowing the pathway to return to its normal, non-pseudo-hypoxic state between doses could potentially mitigate these concerns.
 - Other companies with competing HIF-PH inhibitors in development appear to be pursuing once-daily dosing at this time.

Complete loss of PHD2 has been shown to cause heart failure in mice; however partial and intermittent inhibition with a drug may be different

- Minamishima et al. (2008) reported that somatic inactivation of PHD2 in mice cause polycythemia, leading to hyperviscosity and, in turn, thrombosis and cardiac failure.
- However, it is precisely this mechanism that causes the erythropoietic benefit of the PHD inhibitors, and we believe it is unlikely that pharmacologic inhibition by roxadustat (particularly at the intermitted doses noted previously) will lead to the same cardiac dysfunction that was seen with the complete loss of PHD2 function seen in these mice.
- Additionally, in Phase II studies, roxadustat showed a potential CV benefit in lowering LDL (which may have more meaning given the recent confirmation of the LDL-hypothesis by the IMPROVE-IT study).
- Roxadustat has also shown a neutral (and potentially even beneficial) effect on blood pressure.
- Safety analyses across four Phase II trials did not reveal any association between the rates of occurrence of CV events with roxadustat dose, rate of Hb rise, or Hb level.

A Swiss study shows a lower mortality from coronary heart disease and stroke at higher altitudes

- Using mortality data from 1.64M German Swiss residents (corresponding to 14.5M person-years), Faeh et al. (2009) found a protective effect of living at higher altitude on both coronary heart disease (CHD) and stroke mortality.
 - Per 1000 meters of elevation:
 - The relative risk of CHD decreased by 22%
 - The relative risk of stroke decreased by 12%
- This effect tended to be stronger in men than in women and for CHD than for stroke.
- Additionally, it was found that being born at altitudes higher or lower than the place of residence was associated with lower or higher risk, respectively.
- The authors concluded that these differences were unlikely to be due to classical risk factors but may be a result of differences in climate, diet, or both.

Table 2. Number of Deaths Resulting From CHD and Stroke and Corresponding Age-Standardized Mortality Rates (per 100 000 Person-Years) With 95% CIs, 1990 to 2000, in German Switzerland in Subjects 40 to 84 Years of Age*

Residence,† m Above Sea Level	Person-Years	CHD			Stroke		
		Deaths	Rate	95% CI	Deaths	Rate	95% CI
Men							
<300	383 642	1505	289	275–304	407	72	65–79
300–600	5 641 604	19 477	286	282–291	6072	82	80–84
600–900	824 056	3141	290	280–300	927	78	73–83
900–1200	130 181	506	273	249–297	177	81	69–93
1200–1500	64 908	217	246	213–279	67	70	53–87
>1500	31 479	97	242	193–290	31	68	44–91
Total (259–1960)	7 075 870	24 943	286		7681	80	
Women							
<300	435 982	892	104	97–111	391	43	39–47
300–600	6 027 854	10,881	105	103–107	6062	56	55–57
600–900	796 301	1,688	108	103–114	899	58	54–61
900–1200	106 325	227	98	86–111	138	57	47–66
1200–1500	54 663	96	92	73–110	69	66	50–81
>1500	27 997	41	74	52–97	24	50	30–69
Total (259–1960)	7 449 122	13 825	104		7583	55	

n=1 382 029. Data source: Swiss Federal Statistical Office/Swiss National Cohort.

*Only those whose place of birth was in the same altitude range (ie, ±200 m) as their place of residence in 1990.

†In 1990.

A US study shows that high altitude is associated with lower mortality in incident dialysis patients and the impact is more profound than the overall population

- Using USRDS data, Winkelmayer et al. (2009) looked at 804,812 patients who initiated dialysis and were followed up for a median of 1.78 years.
- After multivariable adjustment, compared with patients living at an altitude of lower than 76 meters, the relative mortality rates were:
 - 0.97 for those living from 76 through 609 m,
 - 0.93 for those living from 610 through 1218 m,
 - 0.88 for those living from 1219 through 1828 m, and
 - 0.85 for those living higher than 1828 m.

Table 3. Age- and Sex-Standardized Mortality Rates in the US General and Dialysis Populations

Residential Elevation, m	General Population	United States Renal Data System
Standardized mortality rates (95 CI) ^a		
Rates per year		
<76	0.01131 (0.01130 to 0.01132)	0.15793 (0.15699 to 0.15886)
76-609	0.01188 (0.01187 to 0.01189)	0.15476 (0.15397 to 0.15554)
610-1218	0.01153 (0.01150 to 0.01156)	0.15406 (0.15050 to 0.15762)
1219-1828	0.01108 (0.01105 to 0.01112)	0.13474 (0.13074 to 0.13874)
>1828	0.01048 (0.01041 to 0.01056)	0.13456 (0.12637 to 0.14275)
Rate ratios		
<76	1.0 [Reference]	1.0 [Reference]
76-609	1.050 (1.049 to 1.051)	0.980 (0.972 to 0.988)
610-1218	1.019 (1.016 to 1.021)	0.976 (0.952 to 0.999)
1219-1828	0.980 (0.977 to 0.983)	0.853 (0.828 to 0.879)
>1828	0.927 (0.920 to 0.933)	0.852 (0.802 to 0.906)
Rate differences per 100 000 person-years		
<76	1.0 [Reference]	1.0 [Reference]
76-609	57 (55 to 58)	-317 (-194 to -439)
610-1218	21 (18 to 25)	-386 (-18 to -755)
1219-1828	-23 (-19 to -26)	-2319 (-1908 to -2729)
>1828	-83 (-76 to -91)	-2336 (-1512 to -3160)

Abbreviation: CI, confidence interval.

Metric conversion factor: to convert from meters to feet, divide by 0.3.

^aAll mortality rates were age- and sex-standardized to the general US population living at altitude lower than 76 m.

Key Investment Considerations --

Potential Outcomes of the Phase III Program for Roxadustat and Likelihood that a Superior CV Profile Can Be Shown to the Current Lower Dose of EPO

Roxadustat Phase III efficacy endpoints appear straight-forward and we believe the question is mainly whether the MACE endpoint can be met

- Primary efficacy endpoints:

- Anemia correction studies:
 - US: Hb change from baseline to the average Hb level during weeks 28-52
 - EU: Cumulative % patients with Hb response by week 24. Hb response is defined as Hb of 11 g/dL and an increase of at least 1 g/dL from baseline
- Conversion and maintenance studies:
 - US: Hb change from baseline to the average Hb level during weeks 28-52
 - EU: Hb change from baseline to the average Hb level during weeks 28-36

- Primary safety endpoints:

- **US:** Major cardiac adverse events (MACE)
 - Includes all-cause death, non-fatal myocardial infarction (MI), and non-fatal stroke
 - Pooled across multiple studies
 - Evaluated separately for NDD-CKD and DD-CKD trials
 - Designed to show non-inferiority relative controls with a 10% margin
- **EU:** MACE+ (all MACE endpoints plus hospitalization rates due to heart failure or unstable angina)

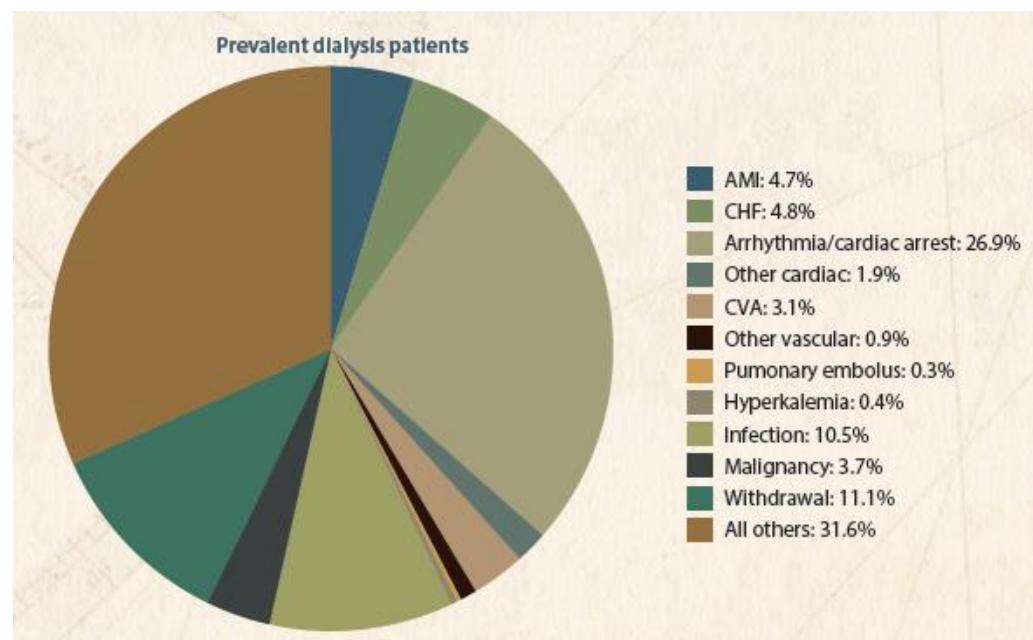
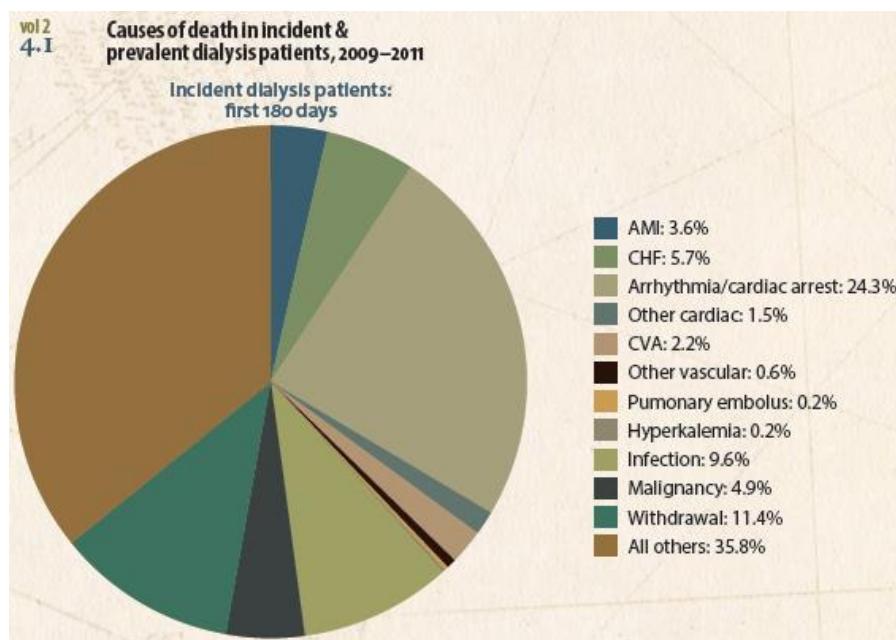
- NDD-CKD trials are comparing roxadustat to placebo
- DD-CKD trials are comparing roxadustat to ESAs (either EpoGen or Aranesp)
 - If non-superiority is met, the two arms are then compared for superiority and the trial is powered to show a 15% superiority

Phase III trials by region	US	EU	China
Total non-dialysis patients	up to 3,800*	up to 1,770*	150**
Total dialysis patients	up to 3,675*	up to 2,250*	300**
Minimum treatment duration	52 weeks	36 weeks	26-52 weeks
Mean treatment duration	~1.3-1.5 years	~1 year	~32 weeks
Total patient years	~10,000+	~4,000	~275

*Some overlap in patient numbers for US and EU (total combined patients = ~7,000 to 8,000)

**Mandatory post-approval safety study of ~2,000 patients expected to be required in China

USRDS data indicates a high overall mortality in the real-world dialysis setting



causes of death

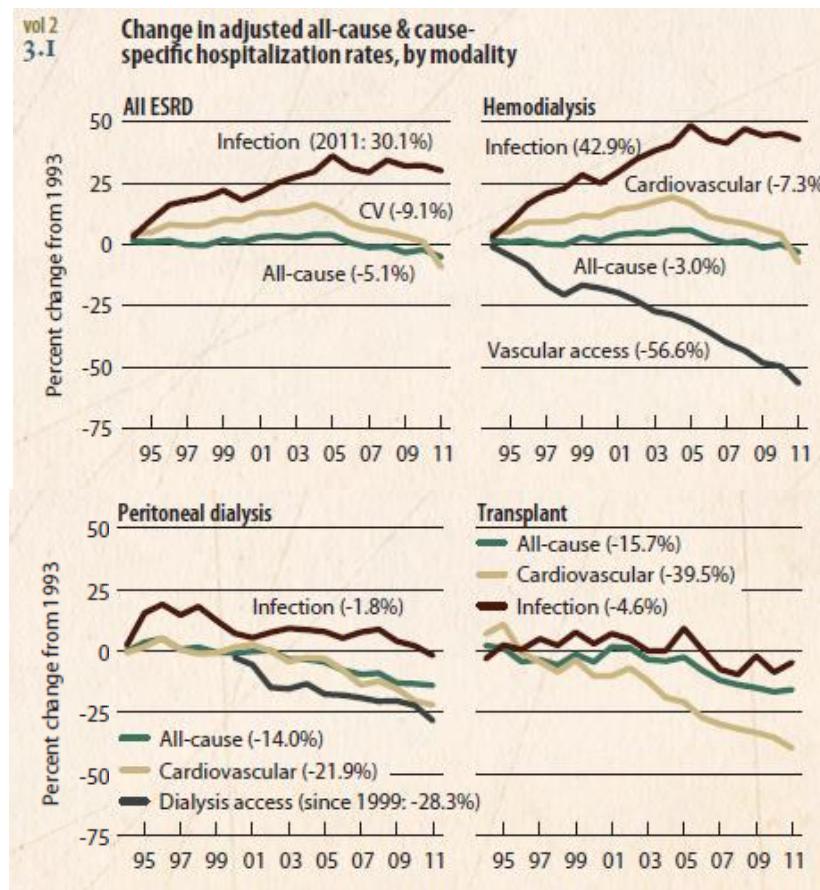
CAUSES OF DEATH IN INCIDENT & PREVALENT DIALYSIS PATIENTS 2009–2011 (FIGURE 4.I)

	incident patients	prevalent patients
overall mortality (per 1,000 patient years)	298	194
percent cardiovascular mortality:		
AMI	3.6%	4.7%
CHF	5.7%	4.8%
arrhythmia/cardiac arrest	24.3%	26.9%
CVA	2.2%	3.1%
other cardiac	1.5%	1.9%

- Overall mortality in the dialysis population:
 - Incident patients: ~15% in first 180 days
 - Prevalent patients: ~19.4% per year
- Approximately 40% of deaths appear to be due to CV related causes.

CV hospitalization rates for hemodialysis patients have declined since the mid-2000s, but remain high compared to peritoneal dialysis and transplant patients

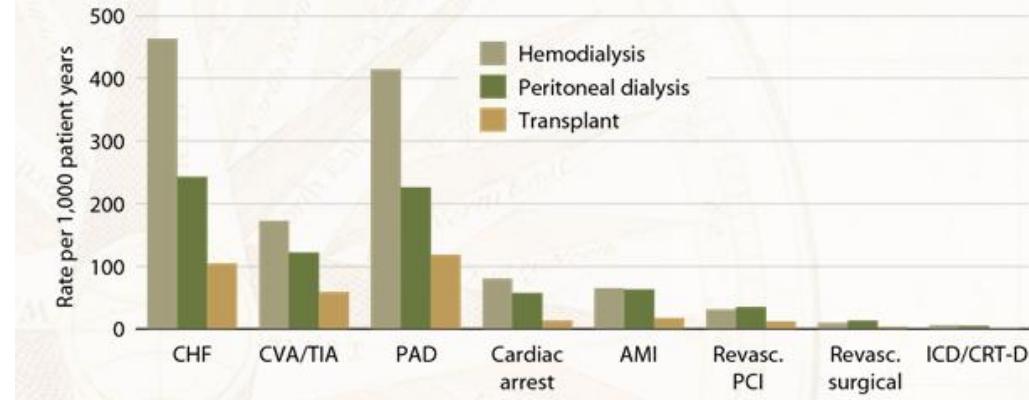
- Per USRDS data, rates of hospitalizations for CV causes increased through ~2004, then began to decline.
- While the decline appears to have started shortly before the publication of the CHOIR and CREATE data and the ensuing decline in ESA use, this likely contributed to the continued decrease through 2011.
- The rates of congestive heart failure (CHF) and peripheral artery disease (PAD) appear in hemodialysis patients appear to be almost twice as high as those in peritoneal dialysis and ~4x as high as with transplant patients. Rates of stroke and transient ischemic attack (TIA) are also elevated in hemodialysis patients.



Source: USRDS 2013 ADR

Event rates of cardiovascular diagnoses & procedures, by modality, 2009–2011

Figure 4.3 (Volume 2)



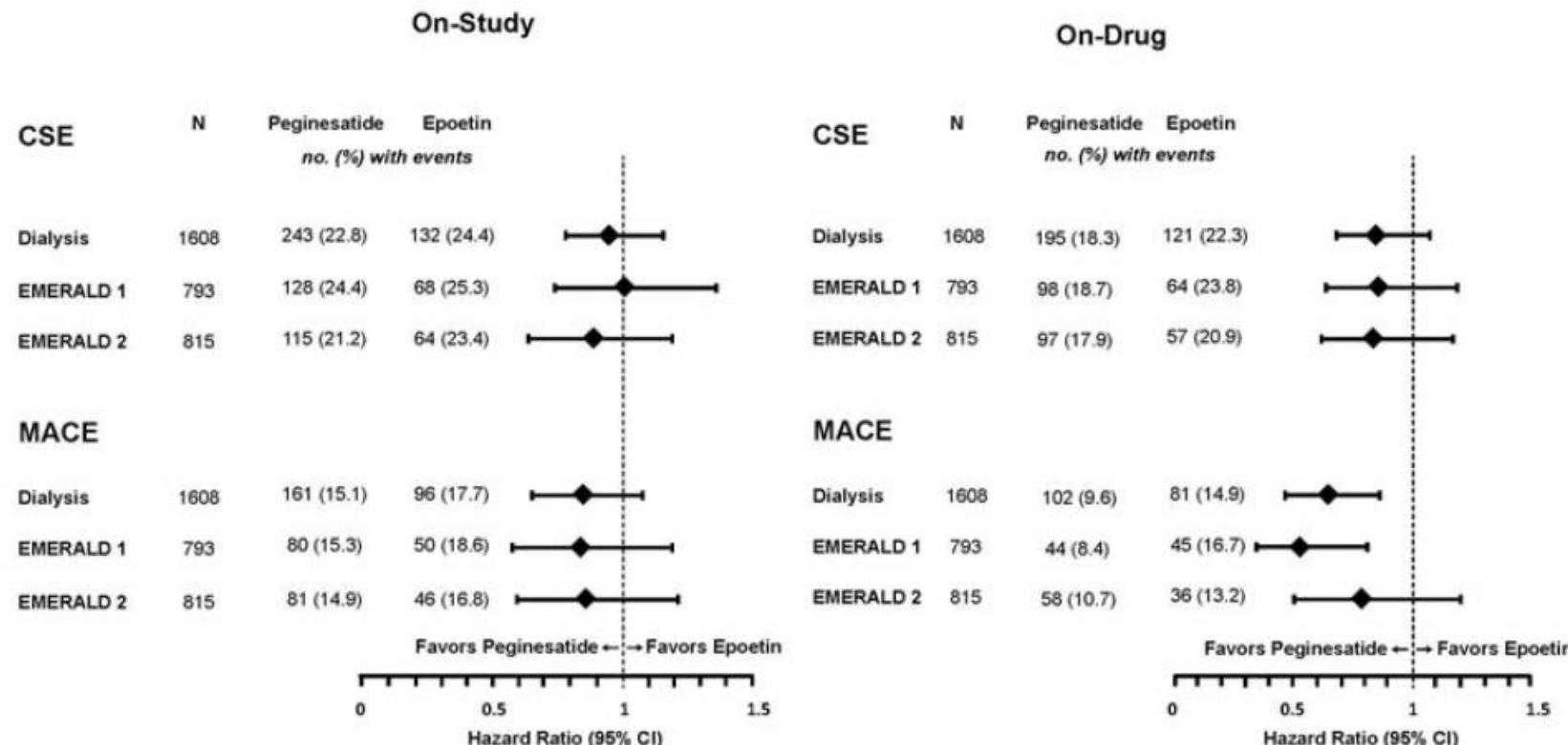
diagnosis of cardiovascular disease

RATES OF CARDIOVASCULAR DIAGNOSES & PROCEDURES, 2009–2011 (RATE PER 1,000 PATIENT YEARS; FIGURE 4.3)

	hemodialysis	peritoneal dialysis	transplant
CHF	464	243	105
CVA/TIA	173	123	59
PAD	415	227	119
cardiac arrest	81	58	14

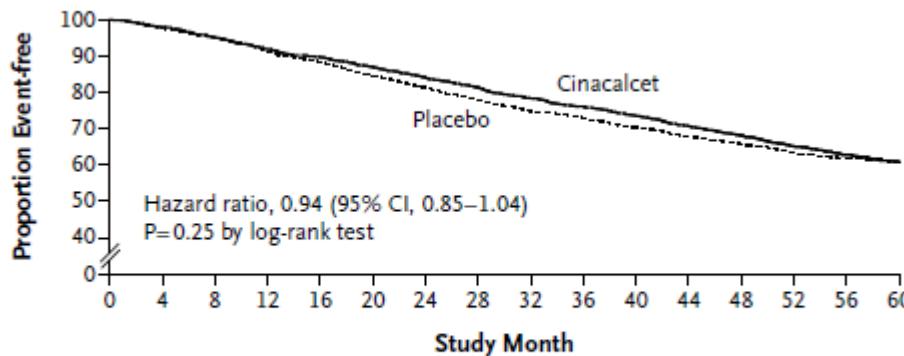
Based on the Phase III Omontys trials, stable hemodialysis patients on EpoGen should have an ~14% annualized MACE event rate in a current-day trial setting

- Given that clinical trials tend to recruit healthier patients with fewer comorbidities, we would expect the mortality and CV event rates in the roxadustat Phase III studies to be lower than those seen in the real-world setting.
- In Omontys' (peginesatide) Phase III EMERALD 1 and 2 trials in dialysis patients, the Composite Safety Endpoint (CSE) included death from any cause, MI, stroke, or serious adverse event of CHF, unstable angina, or arrhythmia. Using this definition, the annualized event rate for patients in the pooled EpoGen arms was ~19%.
- Using the MACE definition from the roxadustat dialysis trials, the annualized event rate in the pooled EpoGen arms was ~14%.
- As the pooled analysis from roxadustat trials will include incident patients as well, we would expect the rate to be slightly higher. FGEN has indicated their powering assumptions are based on a ~16% event rate.



The EVOLVE study showed similar MACE event rates as the EMERALD trials

B Death

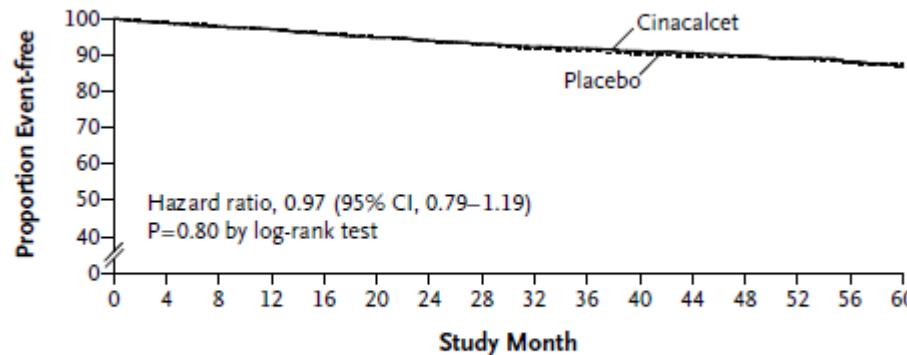


No. at Risk

	Placebo	Cinacalcet
1935	1882	
1828	1754	
1754	1694	
1694	1622	
1622	1559	
1559	1486	
1486	1426	
1426	1388	
1388	1334	
1334	1283	
1283	1232	
1232	886	
886	537	
537	162	
1948	1903	
1845	1779	
1779	1736	
1736	1680	
1680	1621	
1621	1565	
1565	1507	
1507	1462	
1462	1412	
1412	1354	
1354	1292	
1292	899	
899	546	
546	167	

- The EVOLVE trial randomized 3,883 hemodialysis patients with moderate-to-severe secondary hyperparathyroidism to receive either AMGN's Sensipar (cinacalcet) or placebo. There was no statistical difference in outcomes for most of the endpoints studied, including those included in MACE (overall mortality, non-fatal MI, and non-fatal stroke).
- Using the Kaplan-Meier curves for death, MI and the reported number of strokes in the overall trial, we estimated the approximate MACE event rate was similar to that seen in the Epoprostenol arms of the Omontys EMERALD 1 and 2 trials.

C Myocardial Infarction



No. at Risk

	Placebo	Cinacalcet
1935	1857	
1780	1684	
1684	1603	
1603	1521	
1521	1443	
1443	1366	
1366	1298	
1298	1254	
1254	1193	
1193	1136	
1136	1089	
1089	754	
754	463	
463	133	
1948	1877	
1799	1715	
1715	1648	
1648	1579	
1579	1512	
1512	1439	
1439	1377	
1377	1326	
1326	1268	
1268	1204	
1204	1139	
1139	785	
785	466	
466	137	

Event	Total in Trial	Estimated % of Events at end of Year 1	Estimated % of Events at end of Year 2
Death (any cause)	1,421	~10%	~20%
Myocardial infarction	370	~2%	~5%
Stroke	217	~1.5%	~3%
Total MACE events	2,008	~13.5%	~28%

We believe roxadustat stands a good chance of showing superiority to ESAs

- Given the potential CV benefits seen to date with roxadustat (LDL lowering, blood pressure neutrality/lowering) and the evidence suggesting that the CV risks associated with ESA are likely due to the supraphysiologic doses of erythropoietin attained, we believe that roxadustat has a high probability of showing non-inferiority to Epojen and Aranesp in the pooled Phase III dialysis trials, and also stands a good chance of showing superiority on the MACE endpoint.
- Although the Phase II 040 trial included only a small number of patients (66 treated with roxadustat and 22 treated with Epojen) and ran for a relatively short period of time (19 weeks), there appeared to be an numerical imbalance in CV or thrombotic adverse events in favor of the roxadustat arm.
 - All four events in the roxadustat arm were in patients with multiple CV risk factors and were deemed unrelated to the study drug. No information was given for the four events in the Epojen arm.

Table 4. Major Cardiovascular And Thrombotic Events (19 Weeks Treatment, Safety Population)

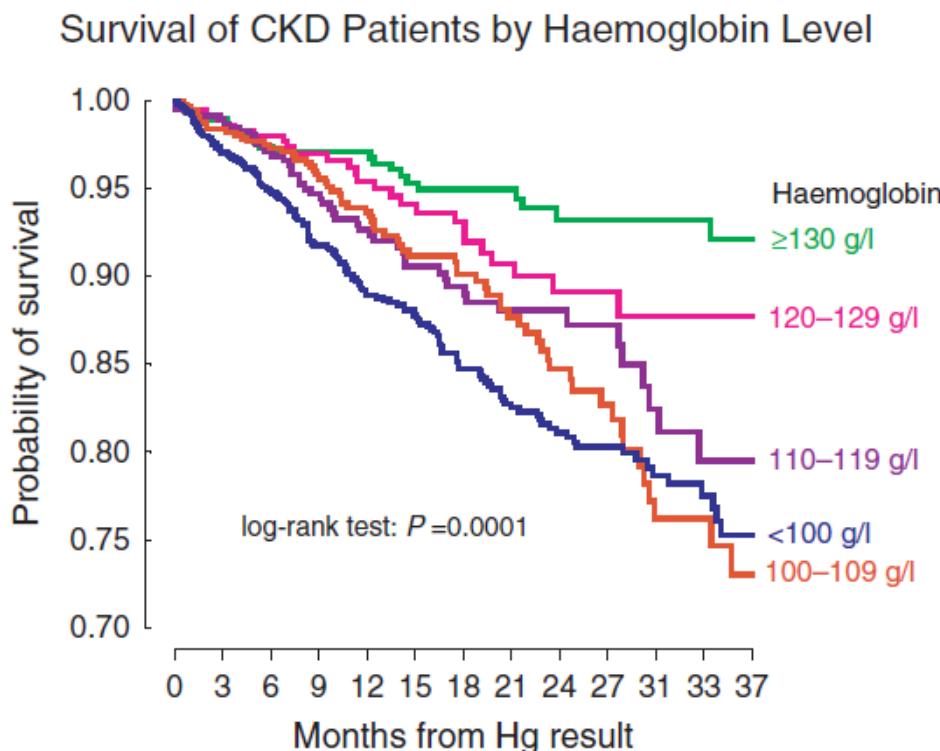
	Subjects (19-weeks)	
	FG-4592 (n=66*)	Epoetin α (n=22)
Patients With ≥ 1 Major CV or Thrombotic Event	4 (6 %)	4 (17.4%)
Sudden Death	1 (1.5%) ^a	0
Myocardial Infarction	0	1 (4.3%)
Cerebrovascular Accident	1 (1.5%) ^b	0
Congestive Heart Failure	1 (1.5%) ^c	1 (4.3%)
Vascular Access Thrombosis	1 (1.5%) ^d	2 (8.6%)

- After speaking with KOLs, we believe that if roxadustat were to show superiority to Epojen/Aranesp in the dialysis setting, it could cause relatively rapid adoption of the drug given the safety issues with ESAs.
- Even if the drug were to show only non-inferiority but with a clear numerical trend in favor of roxadustat, this could also be enough to persuade many dialysis centers to switch.

*Source: Provenzano et al. ASN (2012)

An observational study suggests that higher hemoglobin levels (at least at the time of referral prior to dialysis) may be associated with better outcome

- Levin et al. (2006) analyzed 3,028 stage 3-5 CKD patients (GFR <60 mL/min/1.73m²) from a British Columbia database between 1998 and 2002 showed that those with lower Hb levels had worse survival over the course of ~3 years.
 - 90% of patients with anemia received an ESA at some point during the period
 - 36% of patients without anemia received an ESA at some point during the period
- With roxadustat able to raise Hb, potentially without the CV issues associated with ESAs, we believe it could show a benefit over placebo in the NDD-CKD Phase III trials.
 - FGEN has stated that it expects the average entry Hb in the study to be 9.3 to 9.5 mg/dL, with the median on-study Hb dropping to 8.2 to 8.3 (patients removed from the study after 1-2 doses of ESAs).



- While the control arm is likely to show better survival than is indicated in the real-world database seen here given that clinical trials tend to enroll somewhat healthier patients, the differences in survival by Hb level appear to suggest that there is a relatively good probability that roxadustat could demonstrate superiority over placebo in the non-dialysis setting.
- As noted previously, the anemia market in NDD-CKD patients is much larger than the dialysis market. Even before the results of the CHOIR, CREATE, and TREAT studies reduced the use of ESAs, there was comparatively low use of these agents in this setting due in part to the injectable nature of the drugs.
- As an oral agent, roxadustat has the potential to be more accepted by both patients and physicians.

Overview of the Roxadustat Clinical Program

Roxadustat clinical trials

Anemia Indication	Name	Code	ID	Phase	Current Status	Initiation Date	Last Data	Patients	Comparator	Randomization	Dosing frequency	Location	Lead
Non-dialysis	ALPS	0608	NCT01887600	III	Initiated	Oct-13		450-600	Placebo	2:1	TIW, BIW, QW	EU	Astellas
Non-dialysis	DOLOMITES	0610	NCT02021318	III	Initiated	Apr-14		570	Aranesp	2:1	TIW, BIW, QW	EU	Astellas
Non-dialysis	OLYMPUS	001	NCT02174627	III	Initiated	Jul-14		~2,600	Placebo	1:1	TIW	Global	AZN
Non-dialysis	ANDES	060	NCT01750190	III	Initiated	Nov-12		up to 600	Placebo	2:1	TIW, BIW, QW	US, Asia-Pac., LA	FibroGen
Non-dialysis	Phase III (China)	808	-	III	Planned	1H:15	2H:16	150	Placebo	2:1	TIW	China	FibroGen
Non-dialysis	Phase II (Japan)	0303	NCT01964196	II	Initiated	Oct-13		100	Placebo			Japan	Astellas
Non-dialysis	Phase IIb (China)	047	NCT01599507	IIb	Completed	May-12	Nov-13	91	Placebo			China	FibroGen
Non-dialysis	Phase II	017	NCT00761657	II	Completed	-	Nov-10	116	Placebo			Japan	FibroGen
Non-dialysis	Phase II	041	NCT01244763	II	Completed	Nov-10	Jun-12	145	-			US	FibroGen
Dialysis (incident)	HIMALAYAS	063	NCT02052310	III	Initiated	Feb-14		up to 750	Epogen	1:1	TIW	Global	FibroGen
Dialysis (stable)	ROCKIES	002	NCT02174731	III	Initiated	Jul-14		1425	Epogen	1:1	TIW	Global	AZN
Dialysis (stable)	Phase III (N. America)	064	--	III	Planned	--		up to 750	Epogen	1:1	TIW	N. America	FibroGen
Dialysis (stable)	Phase III (EU)	0613	--	III	Planned	--		750	Epogen/Aranesp	356:200:174	TIW	EU	Astellas
Dialysis (stable)	Phase III (China)	806	-	III	Planned	1H:15	2H:16	300	Epogen	2:1	TIW	China	FibroGen
Dialysis	Phase II (China)	048	NCT01596855	II	Completed	Sep-11		96	Epogen			China	FibroGen
Dialysis	Phase II	040	NCT01147666	II	Completed	Jun-10	Nov-12	159	Epogen/Placebo			US	FibroGen
Dialysis	Phase II (Japan)		NCT01888445	II	Initiated	May-13		120	Aranesp			Japan	Astellas
Dialysis	Phase II (with iron)	053	NCT01414075	II	Completed	Aug-11	Nov-13	60	-			US, Russia, Hong Kong, Singapore	FibroGen
Dialysis	Phase I (PK)	203	NCT01083888	I	Completed	Feb-10		12	-			Japan	Astellas
Dialysis	Phase I (PK)	39	--	I	Completed	--		17	Placebo			US	-
Dialysis/non-dialysis	OLE	59	NCT01630889	II/III OLE	Initiated	May-12		150	-			US	Astellas

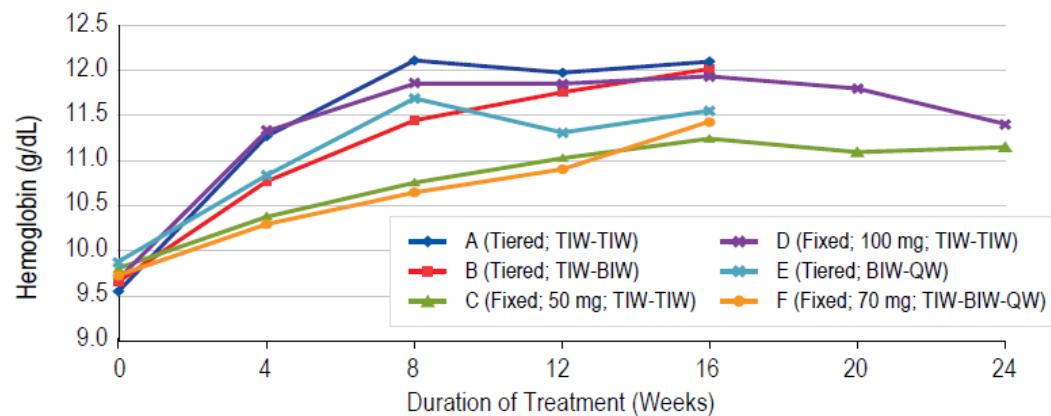
Study 017: Dose Escalating Study in NDD-CKD patients

- A total of 116 patients (96 evaluable) were randomized to receive 1 mg/kg, 1.5 mg/kg, 2 mg/kg, or 0.7 mg/kg of roxadustat dosed twice-weekly (BIW) or thrice-weekly (TIW).
- The dose-dependent change in Hb from baseline in roxadustat patients was statistically significant from placebo by Day 8 ($p=0.025$) and remained so at each assessment through Week 6 ($p=0.0001$ at Day 22; $p<0.0001$ at Day 26–29/end of treatment).
- All patients at the 2 mg/kg dose in both the BIW and TIW groups showed a 100% Hb response rate (defined as achieving an HB rise of 1 g/dL or greater in four weeks). As such, no higher doses of the drug were pursued even in the absence of any dose-limiting toxicities.
- Roxadustat reduced serum hepcidin levels in a dose-dependent fashion.

	Placebo	0.7 mg/kg		1 mg/kg		1.5 mg/kg		2 mg/kg	
		BIW	TIW	BIW	TIW	BIW	TIW	BIW	TIW
N	23	10	12	5	5	10	11	9	11
Mean Maximum Change in Hb	0.44	0.82	1.22	1.12	0.81	1.74	2.03	1.93	2.16
Standard Error of the Mean	0.11	0.28	0.37	0.26	0.45	0.32	0.26	0.22	0.25
% Hb Responder	13%	30%	58%	60%	40%	80%	91%	100%	100%
Median Time to Response (Days)	NA	NA	26.5	42	NA	24.5	14	21	14

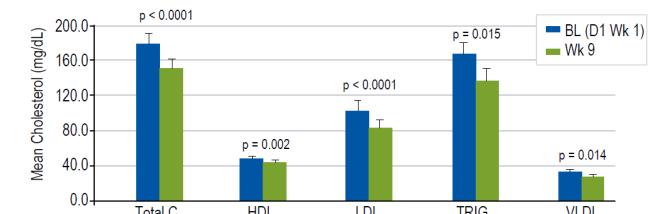
Study 041: Study for Optimization of Starting Dose and Dose Titration in NDD-CKD Patients

- In this open-label study, 145 NDD-CKD patients (143 evaluable) were treated with one of six doses (3 weight-based, 3 fixed) and three dosing frequencies (QW, BIQ, TIW) for 16 to 24 weeks.
- The primary endpoint of Hb response was met (Hb increased $>/=1.0$ g/dL and Hb $>/=11.0$ g/dL at end of treatment). Overall, 92% of patients across cohorts achieved an Hb increase of at least 1 g/dL. These changes were similar for patients with and without inflammation (elevated CRP levels), which are frequently associated with responses to ESAs.
- Hb increases were independent of baseline iron status and required no IV iron supplementation (which was prohibited in all but one patient). In cohorts completing treatment (Cohorts A-D), < 33% of patients (n=27) took oral iron supplements.
- A 30% reduction in mean hepcidin level from baseline with eight weeks of roxadustat treatment ($p=0.0003$) was also observed.
- Decreases in total cholesterol were seen in all cohorts, which rebounded after treatment was completed. Approximately 66% of patients received lipid-lowering agents (63% received statins or fibrates).
- Roxadustat dosed at TIW or BIW did not increase blood pressure in Cohorts A-D. Patients receiving TIW appeared to show decreases in blood pressure. Antihypertensive medications were used by 90% of patients at study entry.



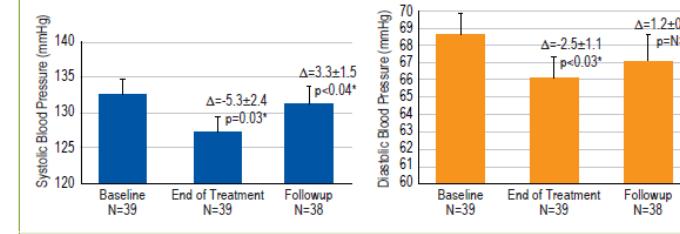
Source: Besarrab et al., ADA 2013; FGEN S1 filing

Figure 7. Mean (\pm SE) Changes in Lipids from Baseline to Week 9 (n=28)



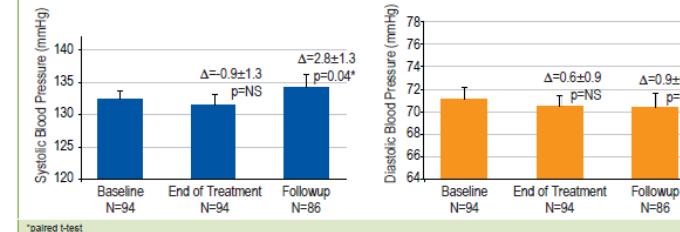
Abbreviations: BL = baseline; C = cholesterol; D1W1 = Day 1 Week 1; dL = deciliter(s); mg = milligram(s); SE = standard error of the mean; Wk = Week. p-values from Signed Rank Test.

Figure 4. Mean (\pm SEM) Blood Pressures at Baseline, End of Treatment, and Followup (FG-4592 TIW)



*paired t-test

Figure 3. Mean (\pm SEM) Blood Pressures at Baseline, End of Treatment, and Followup (FG-4592 TIW or BIW)



*paired t-test

Table 1. Phase 2 FG-4592 Dosing Schedule

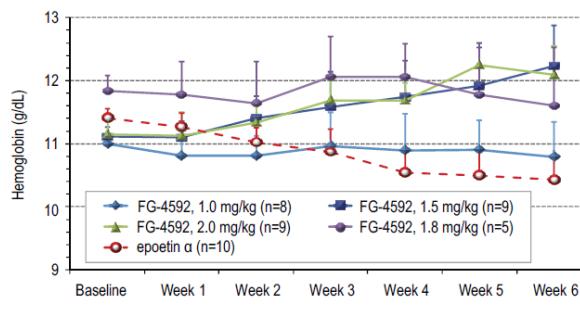
Cohort*	Treatment Duration (weeks)	FG-4592 Starting Dose (mg)			Correction and Maintenance Dosing
		Low Weight (40-60 kg)	Medium Weight (> 60-90 kg)	Heavy Weight (> 90-140 kg)	
A	16	60	100	140	TIW-TIW
B	16	60	100	140	TIW-BIW
C	24	-	50	-	TIW-TIW
D	24	-	100	-	TIW-TIW
E	24	70	100	150	BIW-QW
F	24	-	70	-	TIW-BIW-QW

Abbreviations: TIW = thrice weekly; BIW = twice weekly; QW = once weekly; kg = kilogram(s); mg = milligram(s); N = number of patients. *For Cohorts A-E, N = 24; for Cohort F, N = 25.

Study 040: ESA Conversion Study in DD-CKD Patients

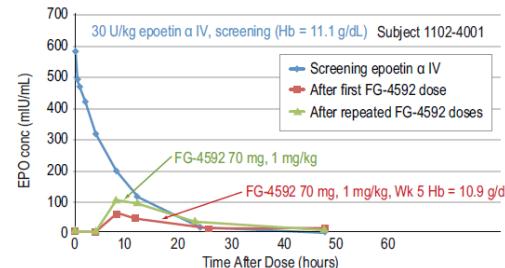
- Part 1 was a 6-six week study of 54 hemodialysis patients (42 evaluable) who were receiving prior Epogen. These patients were randomized to receive 4 sequential doses of roxadustat or continuing prior Epogen doses.
- Part 2 was a 19-week study in 90 patients (83 evaluable) to establish optimal conversion doses and dose adjustments.
- The primary endpoint of maintained Hb at the end of the study period was met in both arms. IV iron supplementation was prohibited.
- In the 6-week portion, hepcidin levels were significantly lower in the roxadustat arm compared to the Epogen arm. In the 19-week portion, changes in ferritin levels were similar between arm, but a greater reduction in transferrin saturation (TSAT) was seen with Epogen. The study also showed an improvement in mean reticulocyte Hb content (CHr) compared to placebo.
- Total cholesterol levels were reduced by an average of 10-20% (and up to 60%) from baseline in the roxadustat arm, which was sustained for the 19-week portion of the study and was significant compared to the Epogen arm (which showed no reduction) over the study period ($p<0.05$).
- Plasma EPO levels were also much lower with roxadustat therapy than during prior ESA treatment within the same patient.

Figure 2. FG-4592 Maintains/Increases Hemoglobin Level In A Dose-Dependent Manner [Mean (\pm SE) Hemoglobin Over Time (*EE Population) In FG-4592 Subjects And In Epoetin α Subjects Treated For 6 Weeks]



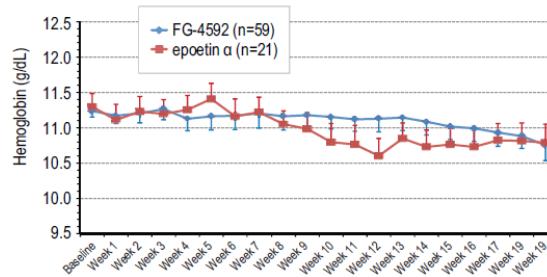
*Efficacy Evaluable: Patients received study treatments for at least 4 weeks.

Figure 6. Plasma EPO Level During Treatment With Therapeutic Dose Of FG-4592 Is Much Lower Than During ESA Treatment Within The Same Subject While Hemoglobin Level Was Maintained



Source: Provenzano et al., ASN 2012; FGEN S1 filing

Figure 5. FG-4592 Maintains Hemoglobin Level Over 19 Weeks [Mean (\pm SE) Hemoglobin Over Time (*EE Population) In Pooled FG-4592 Subjects And In Epoetin α Subjects Treated For 19 Weeks]



*Efficacy Evaluable: Patients received study treatments for at least 4 weeks.

Figure 8. No Functional Iron Deficiency Without Reduction In Reticulocyte Hemoglobin Value In Patients Treated With FG-4592, Despite No IV Iron Supplementation

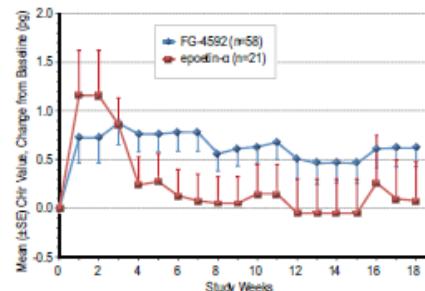
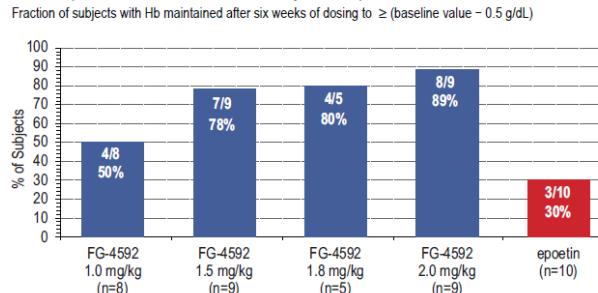
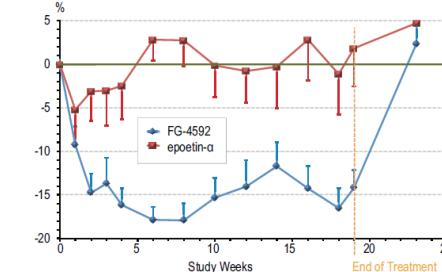


Figure 3. FG-4592 Is Superior To Epoetin α In Correcting Hemoglobin Levels (6 Weeks Treatment, *EE Population)



*Efficacy Evaluable: Patients received study treatments for at least 4 weeks.

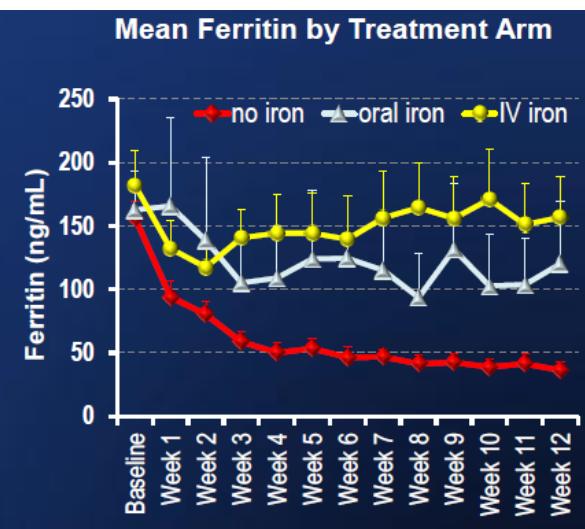
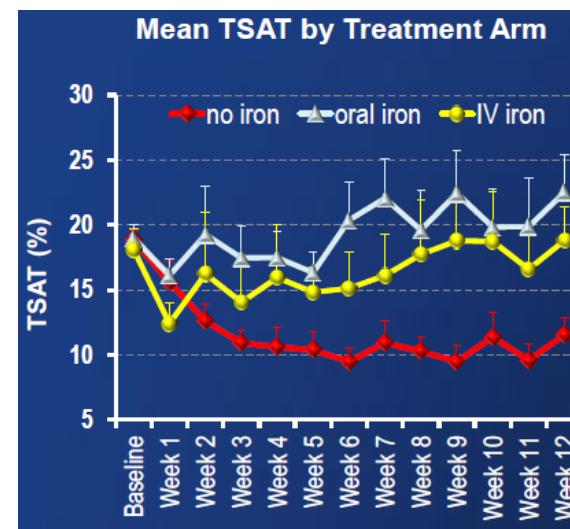
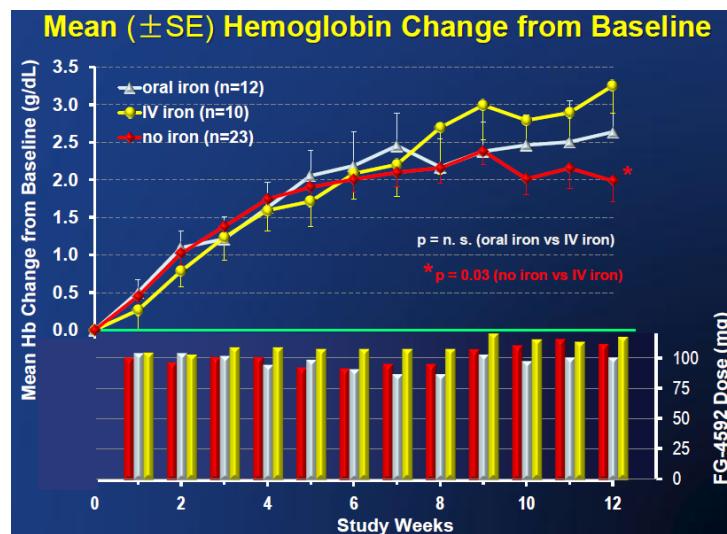
Figure 9. FG-4592 Treatment Resulted In Significant Reduction In Total Cholesterol From Baseline (Mean (\pm SE) Percent Change)*



*Subjects were not required to fast before blood collection. The reduction in total cholesterol was significantly different between the FG-4592 and epoetin treatment arms throughout the Dosing Period ($p<0.05$, Wilcoxon Rank Sum test)

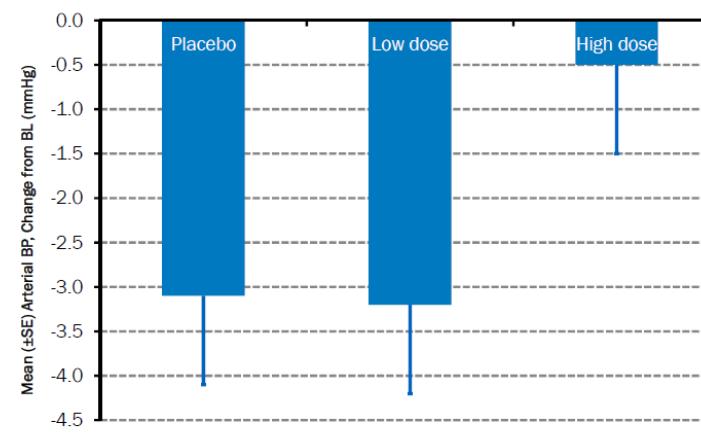
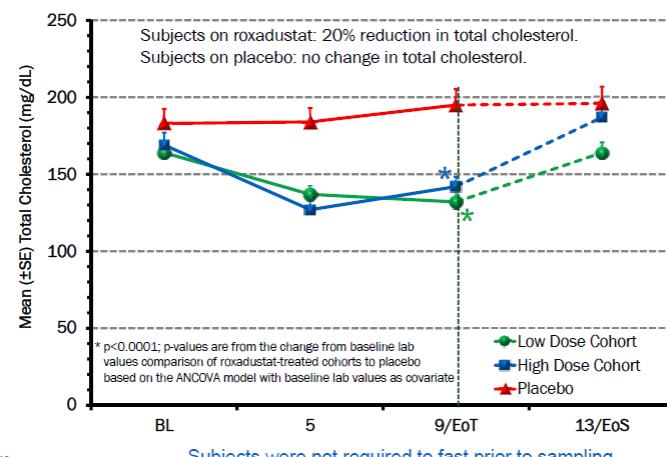
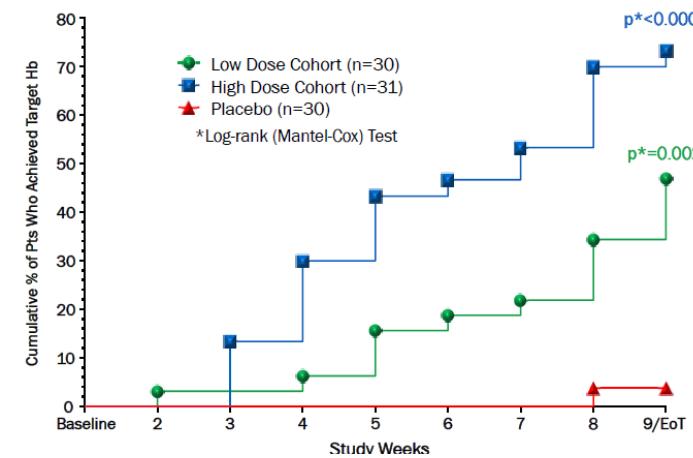
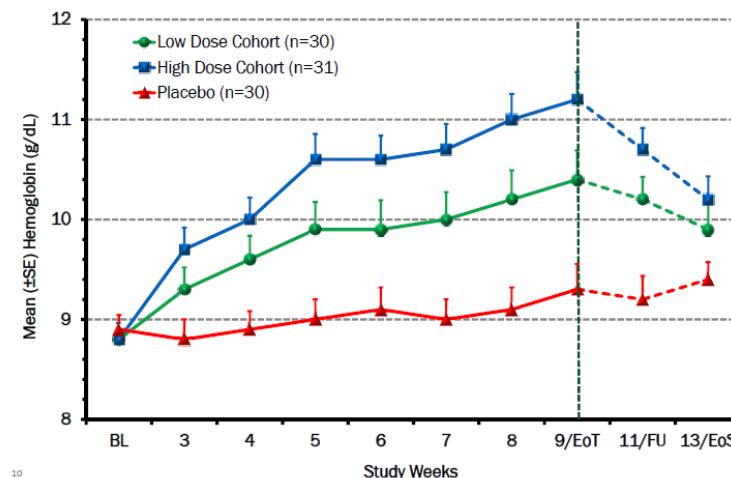
Study 053: Correction of Anemia in Incident Dialysis Patients

- This open-label trial enrolled 60 incident dialysis patients (55 efficacy evaluable) who were on dialysis for at least two weeks and not more than four months and had not been treated with ESAs. Patients were treated with the same tier-weight based dosing regimen utilized in Study 041 for 12 weeks. The 48 hemodialysis (HD) patients were randomized to one of the three iron supplementation options: oral iron, IV iron, or no iron. The 12 peritoneal dialysis (PD) patients received oral iron.
- All treatment groups met their primary endpoint in increasing Hb level during treatment, with maximum mean Hb increases from baseline, ranging between 2.8 g/dL to 3.5 g/dL. Over 90% of patients achieved greater than a 1 g/dL increase in Hb at week 12.
- Increases Hb in the IV and oral iron were similar and significantly higher than those in the no iron arm ($p=0.03$), although the no iron arm still showed an ~2.0 g/dL mean increase. The IV and oral iron groups also showed improved mean TSAT and ferritin levels compared to no iron at week 12.
- Similar to study 041, there did not appear to be a relationship between Hb change and serum CRP.



Study 047: 8-Week Placebo-Controlled NDD-CKD (China)

- In this multi-center, double-blind, placebo-controlled study, 91 anemic CKD patients were randomized 2:1 to roxadustat or placebo treatment groups, respectively, in two sequential dose cohorts or placebo. IV iron supplementation was prohibited during the trial, but oral iron was allowed. The study used tier-weight starting dose for four weeks after which the roxadustat dose was adjusted, depending upon the initial response to treatment.
- The primary endpoint of a mean maximum increase from baseline Hb at the end of Week 8 was achieved for both the high and low dose groups. The mean maximum Hb increases at the end of 8 weeks of treatment were 1.6 g/dL and 2.4 g/dL in the low-dose and the high dose cohort, respectively, compared to 0.4 g/dL for placebo ($p<0.0001$ for each vs. placebo).



Source: Qian et al., ASN 2013; FGEN S1 filing

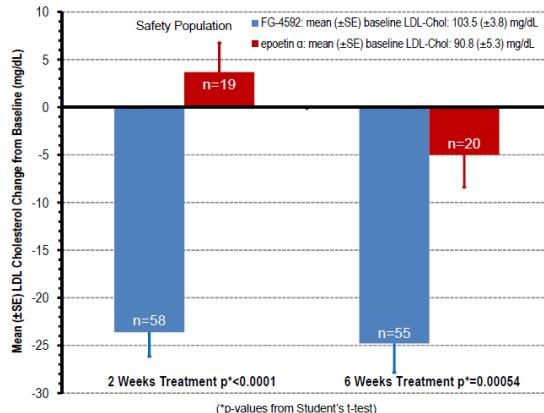
13 Subjects were not required to fast prior to sampling

Study 048: Stable Dialysis Conversion (China)

- In this multi-center, open-label, ESA-controlled study, 84 HD patients (82 efficacy evaluable) with Hb 9 to 12 g/dL previously maintained with ESAs were randomized 3:1 to roxadustat or EpoGen treatment groups, respectively, in three sequential dose cohorts of increasing starting doses of roxadustat.
- The study achieved its primary endpoint, as defined as the number of patients with successful dose conversion whose Hb levels are maintained at no lower than 0.5 g/dL below their mean baseline value at the end of Weeks 5 and 6 (59.1% for the low-dose, 88.9% for the mid-dose, and 100% for the high dose). The low-dose cohort was similar to EpoGen, while the mid- and high-dose arms were statistically superior to EpoGen. Overall, the increases were generally in line with those seen in Part 1 of the US 040 trial.
- Reductions in LDL cholesterol and increases in serum iron were also superior to EpoGen.
- Interestingly, the endogenous EPO levels seen with the mid- and high-doses of roxadustat appeared higher than the low-dose cohort and closer to that seen with EpoGen in the patient described in the 040 trial.

Treatment Arm / Cohort	Safety Set	PK Set	EE Set	Starting Dose Levels by Weight Category			Actual Overall Weekly Dose (Mean ± SD)
				Low-Weight (40 to 60 kg)	Middle-Weight (>60 to 80 kg)	High-Weight (>80 to 100 kg)	
FG-4592	1	25	3	22	70 mg TIW	90 mg TIW	120 mg TIW 4.15 (±0.67) mg/kg
	2	24	3	18	90 mg TIW	120 mg TIW	150 mg TIW 4.77 (±0.95) mg/kg
	3	25	3	20	90 – 100 mg TIW	140 – 150 mg TIW	180 – 200 mg TIW 5.85 (±0.65) mg/kg
Total							4.93 (±1.04) mg/kg
epoetin α				Standard of Care			146.1 ± 12.0 IU/kg

Figure 5: FG-4592 Significantly Reduces LDL Cholesterol



Source: Chen et al. (2013); FGEN S1 filing

Figure 1: FG-4592 Maintains/Increases Hb Level in a Dose-Dependent Manner

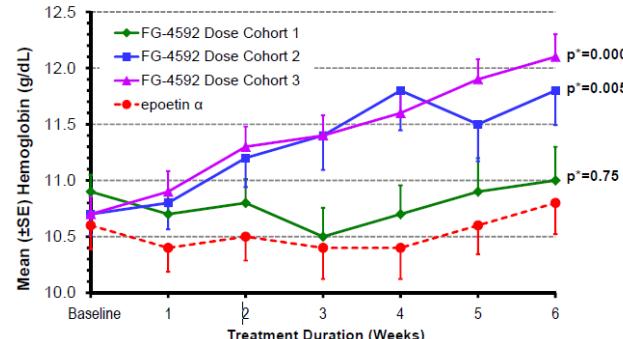
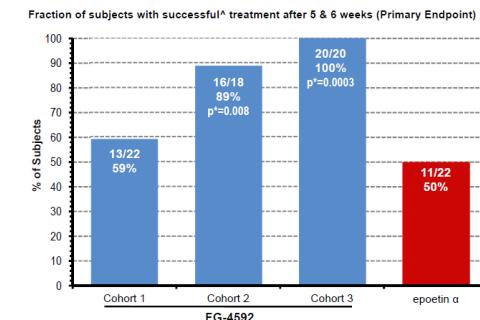


Figure 2: FG-4592 Is Superior to Epoetin α in Maintaining Hb Levels



^aHb maintained at no more than 0.5 g/dL below mean baseline value - LOCF Analysis - EE Population.
p-values are based on Cochran-Mantel-Haenszel test for the comparison between the FG-4592 Cohort and epoetin α group.

Figure 3: FG-4592 Maintains Serum Iron Significantly Better than Epoetin α

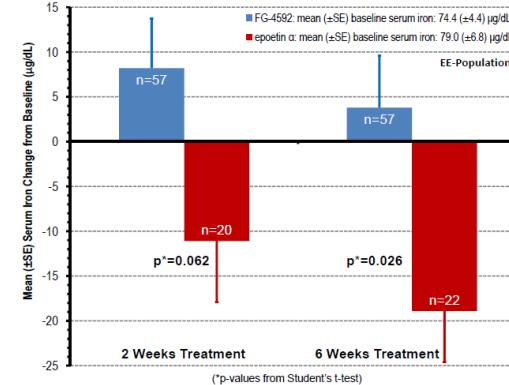
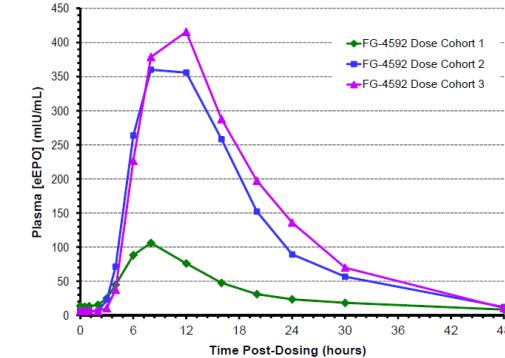


Figure 7: FG-4592 Induces Dose-Dependent Increase in Endogenous EPO Levels



Roxadustat – Adverse events

Dialysis patients – Roxadustat (053 study) compared to Aranesp and EpoGen (historical data)

Studies	Roxadustat FGCL-4592-053*	Darbepoetin Study 211^	
		Darbepoetin	Epoetin α
Sample size	60	91	31
Treatment duration	12 weeks	20 weeks	
# (%) hypertension AEs	6 (10.0%)	28 (31%)	14 (45%)
# (%) patients with SAE	6 (10.0%)	37 (41%)	11 (35%)
Deaths	2 (3.3%)	5 (6%)	1 (3%)

- The SAEs experienced across all roxadustat Phase II trials that were identified by the principal investigator as possibly related to the drug were:
 - One stroke in a patient with a prior history of multiple strokes
 - One incident of vomiting
 - One incident of deep venous thrombosis
- The most commonly reported treatment emergent adverse events (TEAE) in the Phase II studies were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, hypertension and upper respiratory tract infection.
- A Thorough QT study of roxadustat doses up to 5 mg/kg (~4x the average maintenance dose in the NDD-CKD period) showed no effect on QT interval.
- No evidence of hepatotoxicity was observed in any of the roxadustat clinical trials, and the independent data monitoring committee concluded that there was no concern for hepatotoxicity to date. Liver enzymes are being monitored in Phase 3 according to current FDA guidelines, without any special requirements.
- As noted previously, there has been no evidence to suggest tumor risk associated with roxadustat in clinical or preclinical studies to date.

Non-dialysis patients – Roxadustat (041 study)

TEAEs (in $\geq 7\%$ of Patients)	
Adverse Event	n (%)
Peripheral edema	14 (10)
Nausea	12 (8)
Diarrhea	11 (8)
Hypertension	10 (7)
Nasopharyngitis	10 (7)

Serious TEAEs (in $\geq 2\%$ of Patients)	
Adverse Event	n (%)
Congestive heart failure	4 (3)
Pancreatitis	4 (3)
Acute renal failure	3 (2)
Hyponatremia	3 (2)

Competitive Landscape

Roxadustat is potentially first in class among HIF-PH inhibitors

Drug	Company	Indication	Phase
Roxadustat	FibroGen/AZN/Astellas	Anemia (Dialysis)	III
		Anemia (Non-dialysis)	III
AKB-6548	AKBA	Anemia (Dialysis)	II
		Anemia (Non-dialysis)	II
GSK1278863	GSK	Anemia (Dialysis)	II
		Anemia (Non-dialysis)	II
		Aortic Aneurysm	II
		Wound healing	I
Molidustat	Bayer	Anemia (Dialysis)	II
		Anemia (Non-dialysis)	II
DS-1093	Daiichi Sankyo	Anemia (Dialysis)	I
		Anemia (Non-dialysis)	I
JTZ-951	Japan Tobacco	Anemia (Dialysis)	I
AKB-4924	AKBA	IBD	Preclinical
AKB-6899	AKBA	Cancer	Preclinical
		Ophthalmology indications	Preclinical

Data from competing HIF-PH inhibitors

- **ABKA's AKB-6548:**

- A Phase IIb study included 209 non-dialysis CKD (Stage 3-5) patients with anemia who were randomized 2:1 to receive 450 mg QD of AKB-6548 or placebo for 20 weeks. The primary endpoint was defined as achieving or maintaining a mean Hb of ≥ 11 g/dL or increasing Hb by ≥ 1.2 g/dL above the pre-treatment value at weeks 19 and 20.
 - 54.9% of AKB-6548 patients achieved the primary endpoint compared to 10.3% of placebo patients ($p < 0.001$)
 - Only 4.4% of AKB-6548 patients experienced an “excursion” above 13.0 g/dL.
 - Treatment emergent adverse events were similar between arms (74.6% for AKB-6548 vs. 73.6% for placebo).
 - However, there were more serious adverse events with AKB-6548 compared to placebo (23.9% vs. 15.3%, respectively).
 - The most common were renal related.
 - One SAE in the AKB-6548 group was considered probably related to drug treatment and two were considered possibly related. These events were angioedema, elevated liver function tests, and sudden cardiac death (in a patient with multiple risk factors).

- **GSK's GSK1278863A:**

- A Phase IIa dose-ranging study included 107 dialysis and non-dialysis CKD patients receiving 10, 25, 50, or 100 mg of GSK1278863A or placebo once daily.
 - Hemoglobin and erythropoietin levels were increased in the treatment groups relative to baseline and placebo at 15 days.
 - Hepcidin levels decreased in the treatment groups relative to baseline and placebo,
 - Among non-dialysis patients, SAEs were seen in 1/9, 0/17, 2/14, 1/15, and 10/15 patients in the placebo, 10, 25, 50, and 100 mg dose groups
 - Among dialysis patients, SAEs were seen in 0/6, 2/19, and 1/12 patients in the placebo, 10, and 25 mg dose groups.

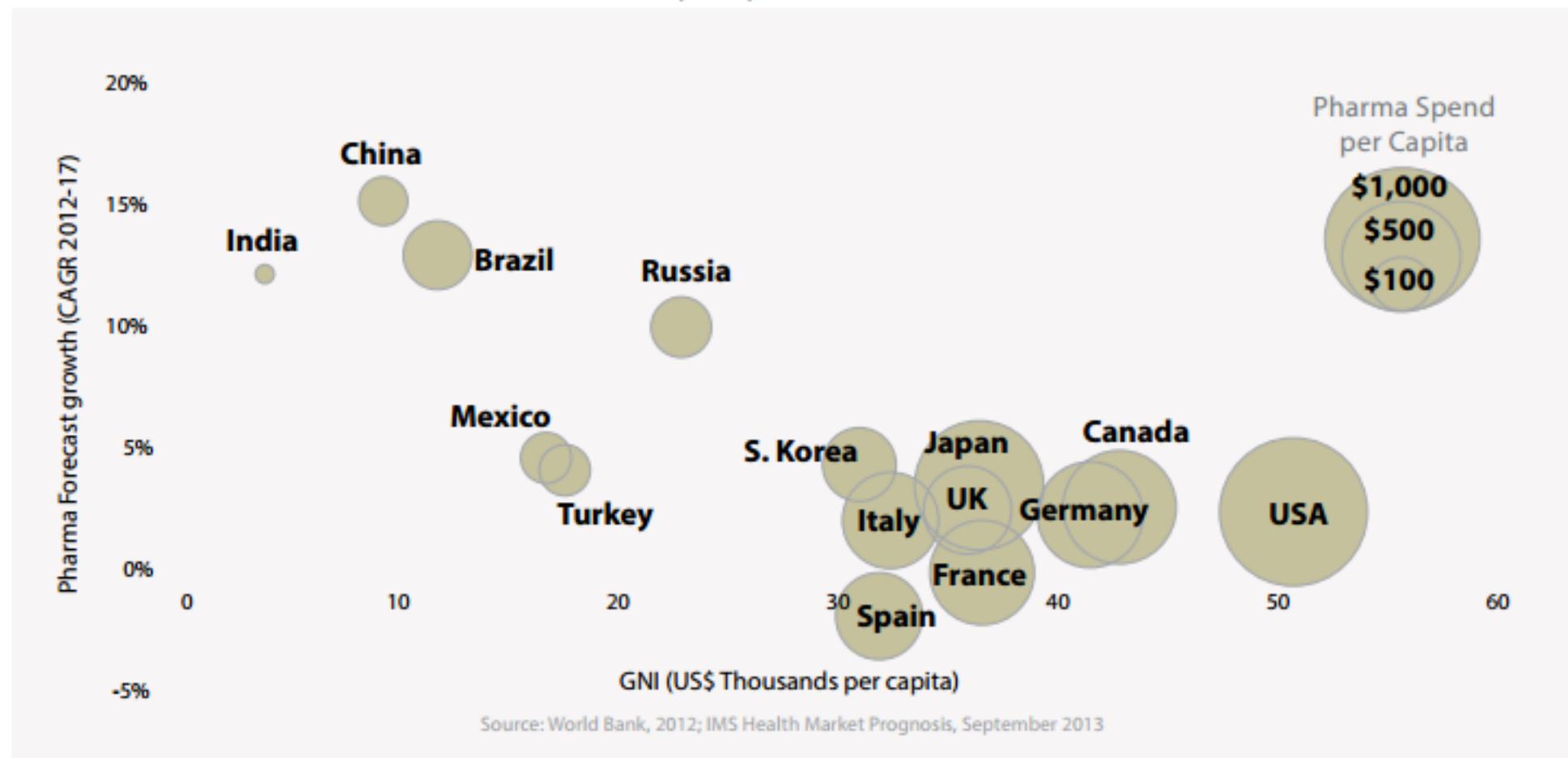
- **Bayer's molidustat:**

- In a Phase I trial of healthy volunteers receiving single doses of molidustat:
 - Significant increases in EPO levels were seen in doses of 12.5 mg and higher
 - Significant increases in reticulocytes were seen in doses of 37.5 mg and higher
 - There were no prohibitive safety findings

Unique China Strategy Targeting One of the Fastest Growing Large Pharmaceutical Markets

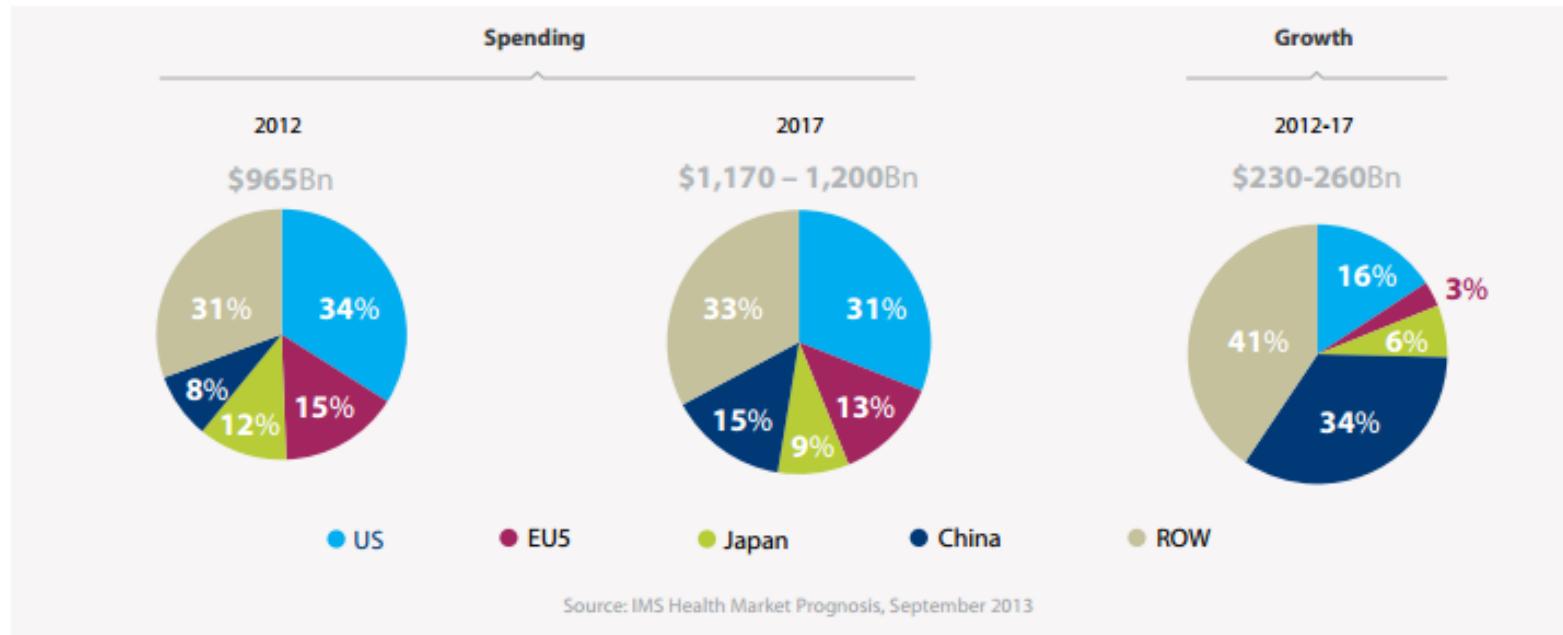
China is the fastest growing major pharmaceutical markets that is now the second largest in the world

Per capita Gross National Income 2012 (GNI) vs. Forecast Pharma Spend



China growth is expected to be a major component of the global pharmaceutical market growth in the coming years

Geographic distribution of medicine spending



Total Healthcare Expenditures

	2006 (\$US)	2011 (\$US)
\$156 billion	\$357 billion	
\$119	\$261	
\$27 billion	\$71 billion	
43%	>95%	
9 th	3 rd	

Per Capita Healthcare Expenditures

Market Size for Pharmaceuticals

Percentage of Population with Health Insurance

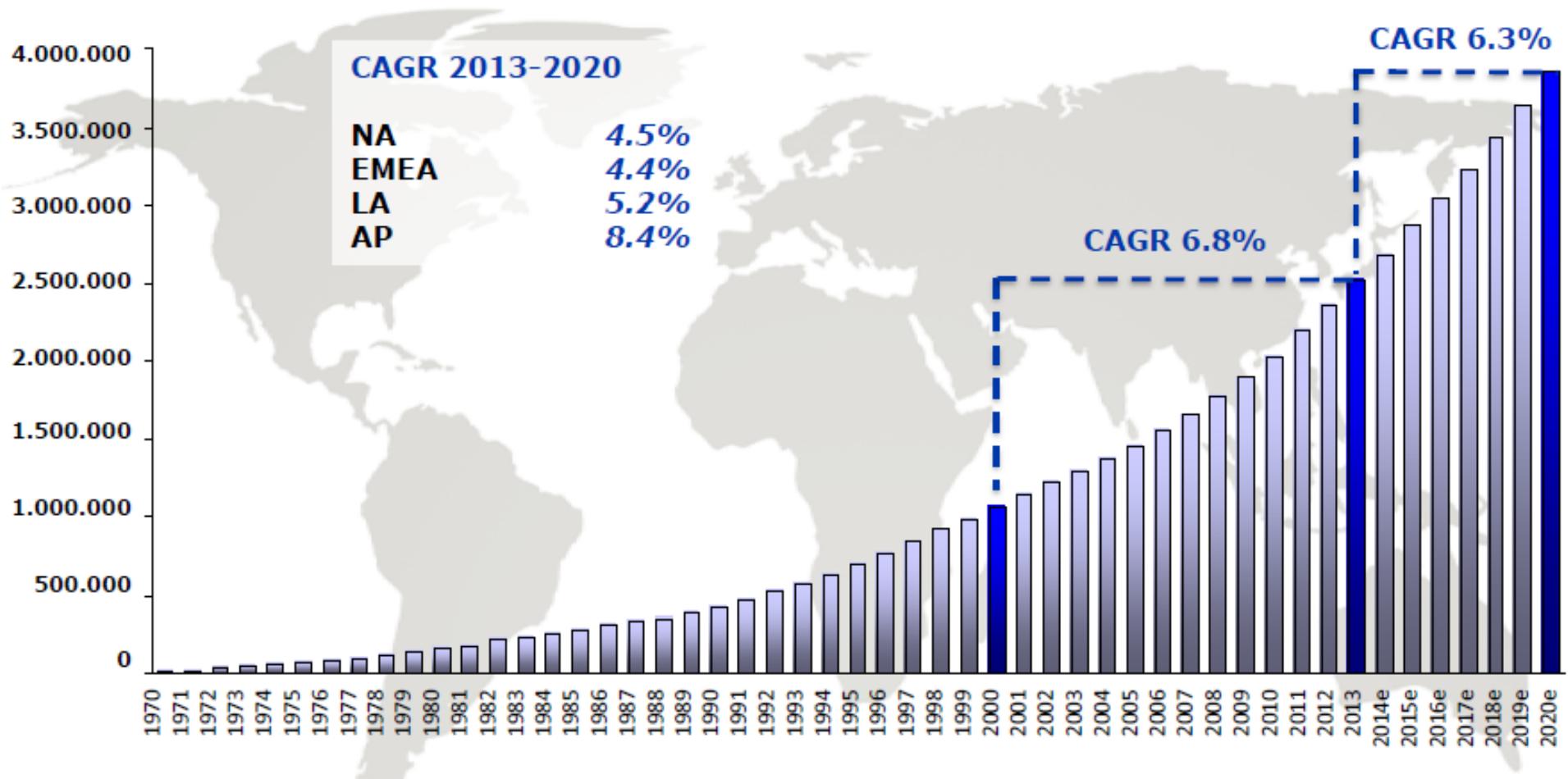
China in Global Ranking of Pharmaceutical Markets

Source: Health care in China: Entering “uncharted waters”, McKinsey & Company, healthcare systems and services practice, November 2012

According to ChinaBio citing IMS data, China has recently overtaken Japan to become the second largest pharmaceutical market in the world. According to ChinaBio projections, becoming the largest drug market – surpassing the US – could come as early as 2020.

Asia Pacific is projected to be the fastest growing geographical region for the global dialysis market

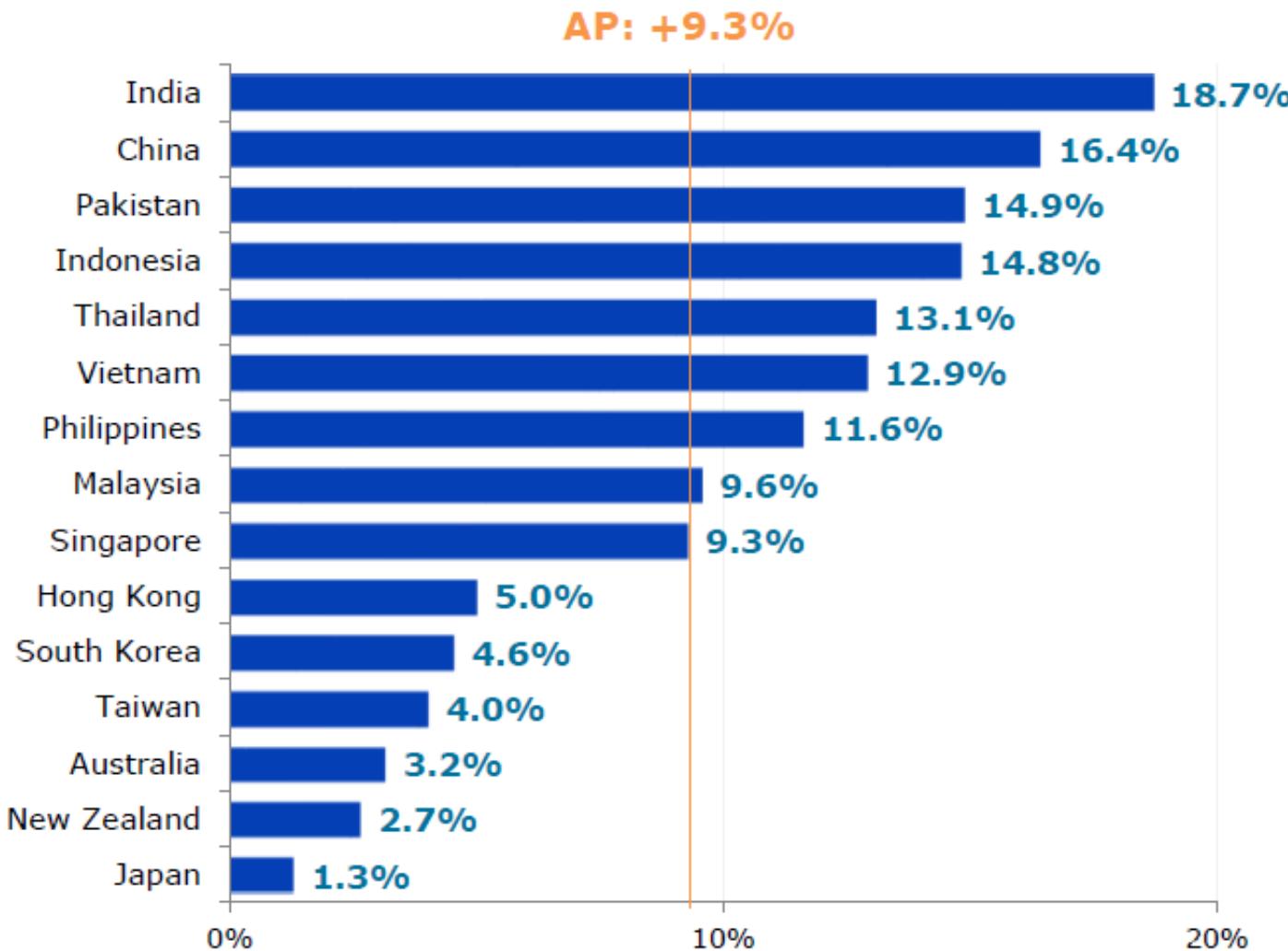
Number of dialysis patients by geographic region and projected growth



NA: North America; EMEA: Europe, Middle East, Africa; LA: Latin America; AP: Asia Pacific ;
CAGR: compounded annual growth rate

China is among the fastest growing dialysis markets

Number of dialysis patients in 2013 vs. 2012 by country in Asia Pacific (AP)



Much room to grow for the Chinese dialysis market driven by the growing economy

Prevalence of CKD is similar in China as compared to the West

USA	13.0%
Norway	10.2%
China	10.8%

However the number of patients on dialysis per million population is significantly lower than more developed economies; within China more affluent coastal regions have higher rate of patients on dialysis; dialysis rates in Taiwan and Hong Kong are several times higher

USA	2,016
Japan	1,892
Korea	664
Phillipines	400
Brazil	356
Taiwan	1,920
Shanghai	552
Beijing	486
Southern China	103
Southwest China	65
Northwest China	27

CKD: chronic kidney disease

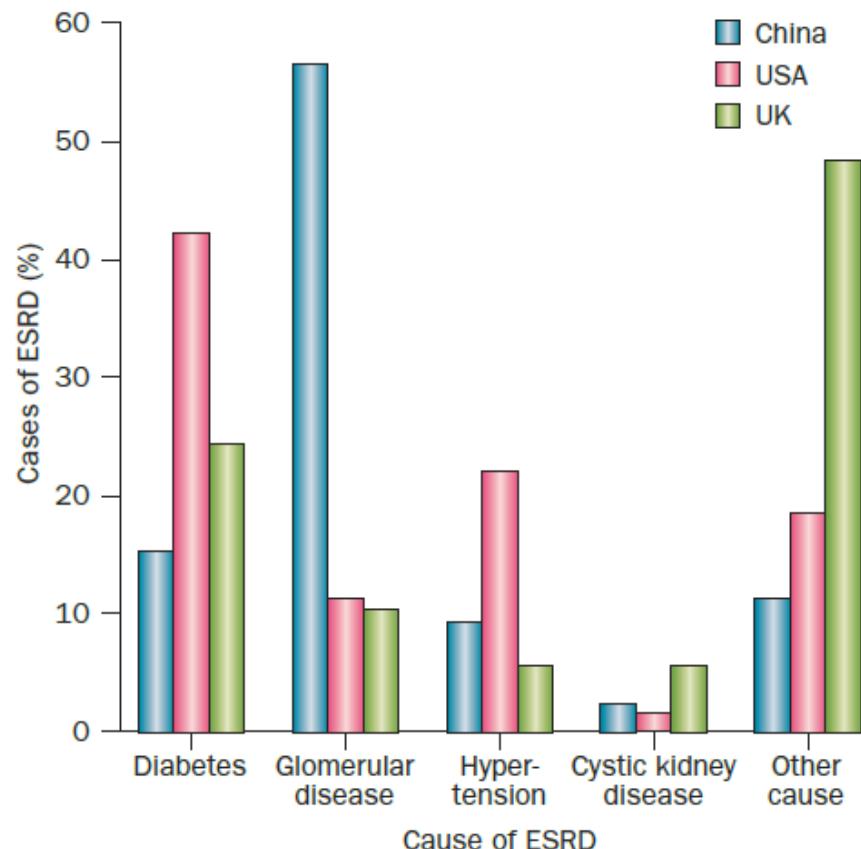
Source: Liu, Nature Reviews Nephrology, 2013; Chen Current Status and Strategies of Blood Purification in China (2012)

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Causes of ESRD are different in China as compared to the West but rapid increase of diabetes in China could further increase the prevalence of ESRD

- Based on data from China Renal Data System, the most common cause of ESRD is glomerular disease (57%) followed by diabetic nephropathy (16%), hypertension (11%), and cystic kidney disease (4%).
- These rates are different from those reported for developed countries such as the USA where diabetic nephropathy is the most common or more frequent cause of ESRD.
- However diabetes is on the rise in China and is becoming a more important contributor of ESRD



ESRD: end-stage renal disease

Source: Liu, Nature Reviews Nephrology, 2013;

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By absolute numbers, the Chinese dialysis market is already large

- Fresenius estimates 400,000 dialysis patients in China, compared to 420,000 in the US
- China dialysis population grew by 16% in 2013 according to Fresenius
- Large majority of estimated 1-2 million ESRD patients not dialed

	United States	China
Dialysis Patients	420,000	350,000 - 400,000 treated during 2013
Total Population	315 Million	1.35 Billion

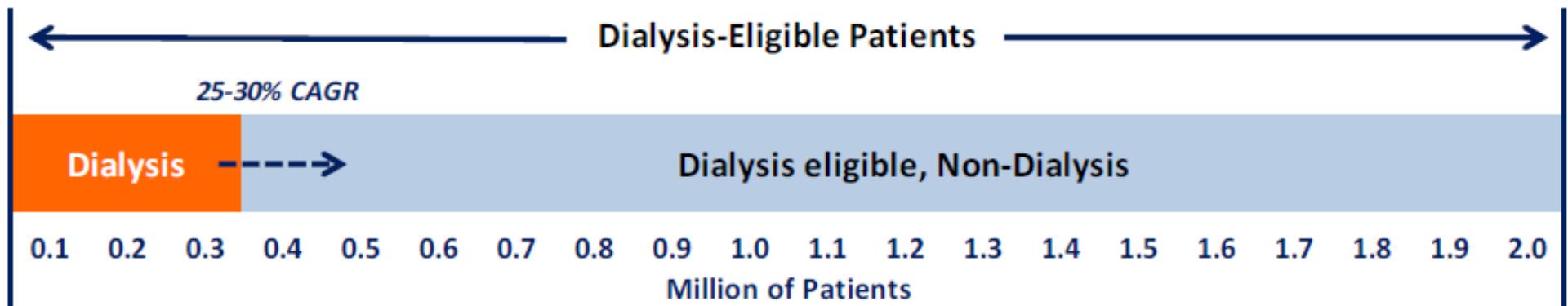
China CKD/ESRD Anemia Market

- Dialysis market:

- According to FibroGen, there are currently 1-2M patients who are considered to be "dialysis-eligible"
 - ◆ Of these, only 300-400K are currently on dialysis
 - ◆ The capacity expansion for dialysis is growing at 25-30% CAGR
 - ◆ Estimated mean hemoglobin levels:
 - At dialysis initiation: 7.0 g/dL
 - Achieved: 9.1 g/dL

- Non-Dialysis CKD market:

- According to FibroGen, there are currently 120M patients in China with CKD
 - ◆ Assuming a similar ratio as in the US, this would imply ~68M Stage 3-4 non-dialysis patients.

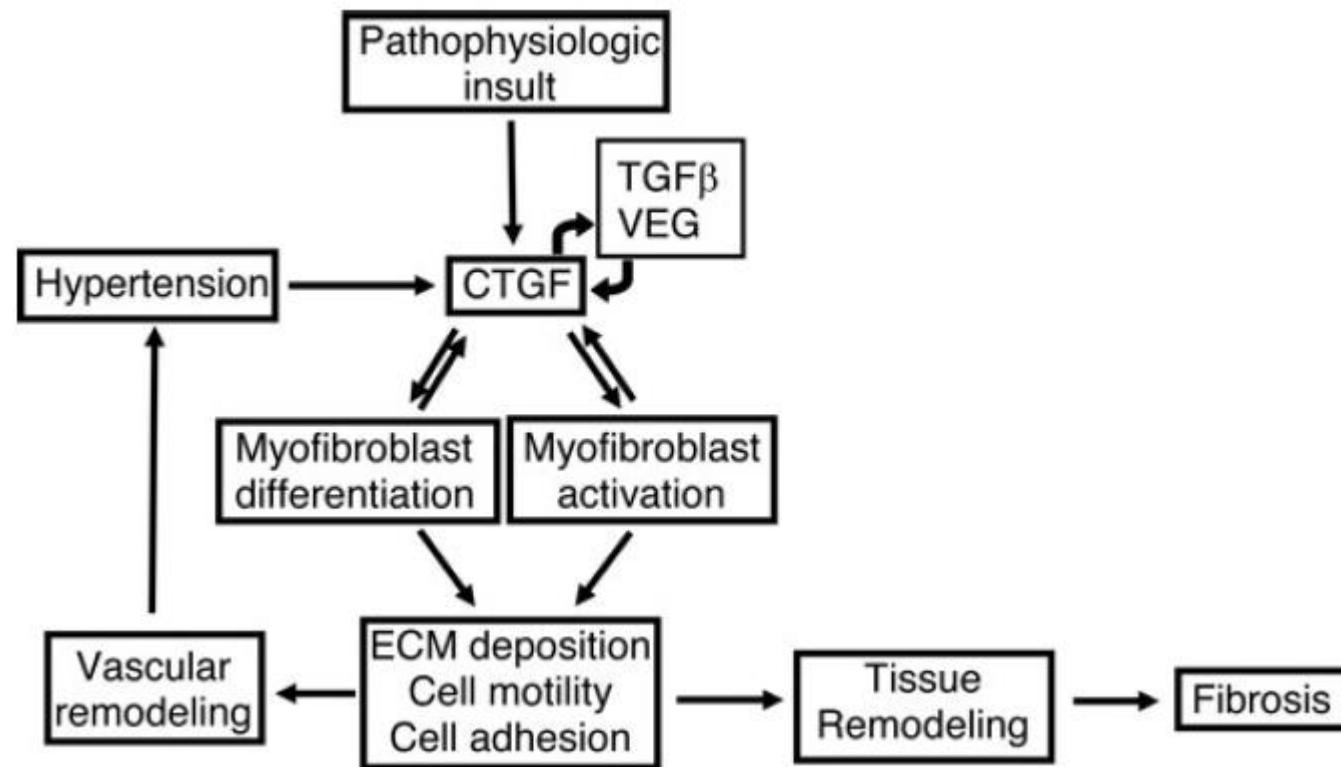


FibroGen has established a wholly owned subsidiary to take advantage of the “green channel” for domestic innovative products

China Trial Advantages
China's clinical trials generally require fewer patients and have shorter duration than the west
New Green Channel and Fast Track paths can potentially speed the approval process
China typically offers much faster patient recruitment and a larger population of treatment-naïve patients
Data produced in China trials can usually be used to support US and European approvals
China pharma are often willing to fund the costs of the trials in China in exchange for China rights
China Trial Challenges
More stringent preclinical requirements than the west (e.g., two species, six-month tox)
No 30-day tacit approval for INDs; approval typically issued in 9-18 months
Clinical trials are conducted only at CFDA approved clinical sites, limiting options
Status of applications are not as transparent as in the west (e.g., no publication of results, silent rejection)
A Chinese legal representative to the CFDA is required (i.e., a foreign company cannot be its own representative)
Potential for issues regarding ownership of the market authorization if not handled properly
Biologics must be manufactured by the seller except for imported drugs; i.e., no biologics may be produced by CMOs

Fibrotic Disease Platform (FG-3019)

FG-3019 is an inhibitor of Connective Tissue Growth Factor (CTGF), a central mediator of fibrosis



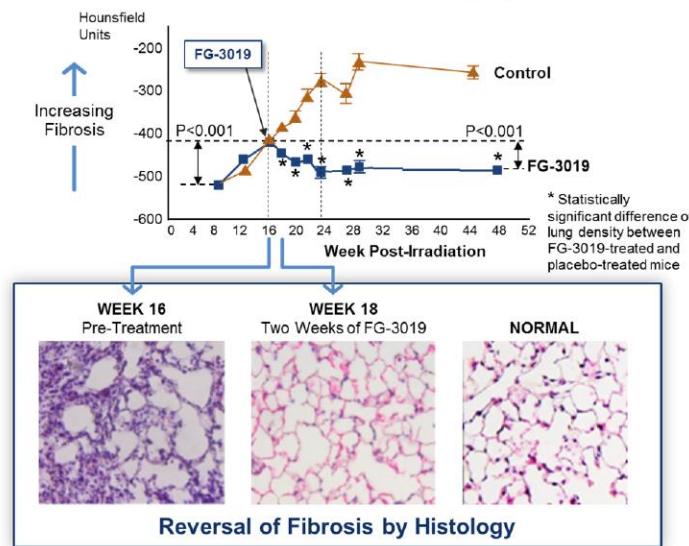
- Fibrosis is the hallmark of many diseases across organ systems, including idiopathic pulmonary fibrosis (IPF), pancreatic cancer, Duchenne muscular dystrophy (DMD), and liver fibrosis.
- Inhibition of CTGF has been shown to reverse fibrosis in animal models.

FG-3019 clinical trials

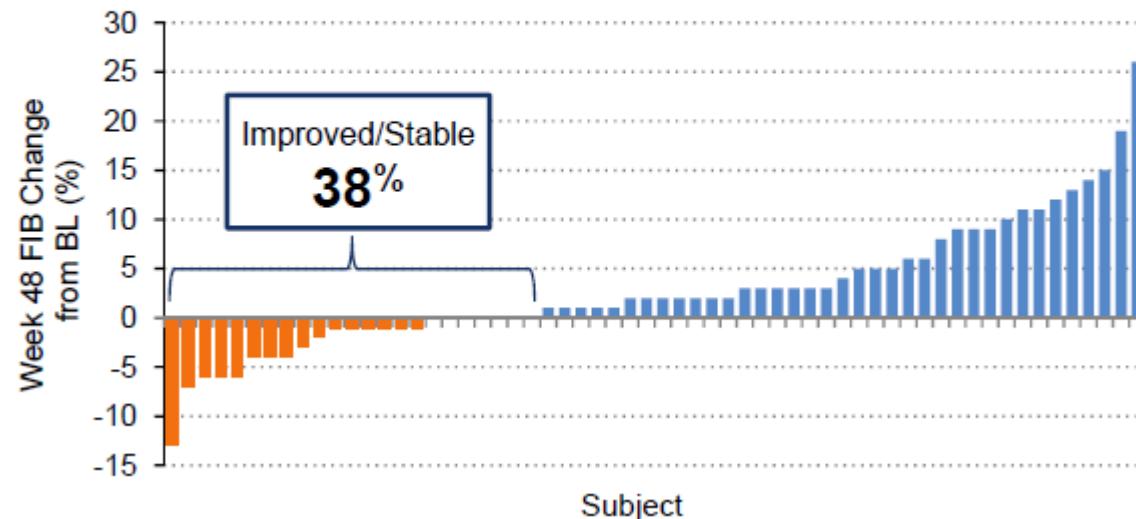
Indication	Study	ID	Phase	Current Status	Initiation Date	Last Data	Patients	Comparator	Location
IPF	067	NCT01890265	II	Recruiting	6/28/2013		136	Placebo	US
IPF	049	NCT01262001	IIa	Completed (extension phase ongoing)	1/12/2011	5/18/2014	89	-	US
IPF	002	NCT00074698	I	Completed	ended in 2004		21	-	US
Pancreatic cancer (Stage 4)	TBD	TBD	II	Advanced planning	2015			TBD	TBD
Pancreatic cancer (Stage 3)	069	NCT02210559	II	Recruiting	7/1/2014		40	Gemcitabine + Abraxane	US
Pancreatic cancer (Stage 3/4)	028	NCT01181245	I/II	Completed	12/1/2008	5/31/2014	75	-	US
Liver fibrosis – HBV	801	NCT01217632	II	Recruiting	2014		120	Placebo	Hong Kong, Thailand
Liver fibrosis – HCV	802	-	II	Recruiting	2014		15	-	Hong Kong
Diabetic Kidney Disease	029	NCT00754143	II	Completed	9/15/2008		38	Placebo	US
Diabetic Kidney Disease	032	NCT00913393	II	Terminated	6/2/2009		46	Placebo	US
Diabetic Kidney Disease	003	NCT00102297	I	Completed	1/26/2007		24	-	US
DMD	TBD	TBD	II	Advanced planning	2015			-	TBD
Radiation control measures	TBD	TBD	NHP	Under discussion	TBD			TBD	TBD

FG-3019 has been shown to reverse lung fibrosis in both IPF patients and mouse models

Reversal of Fibrosis by Micro-CT Imaging



Lung Fibrosis Change by High Resolution CT at Week 48 – reversal never previously observed



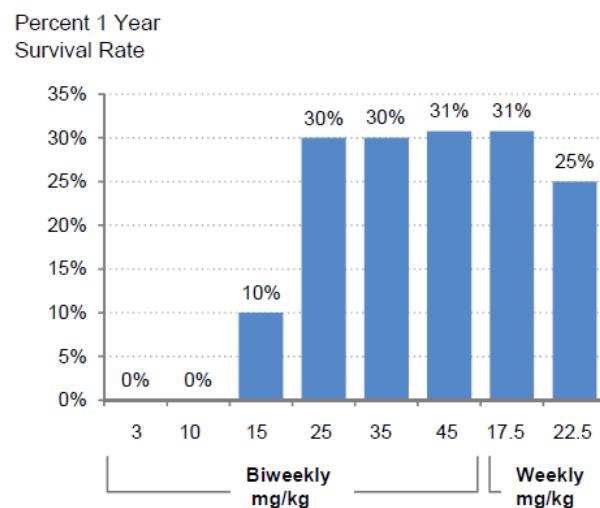
- Reversal of fibrosis and improved survival were seen with FG-3019 in a radiation-induced lung fibrosis mouse model
 - When FG-3019 was initiated 20 days after exposure, 70% of mice survived despite having received a lethal dose radiation.
- In humans, 89 IPF patients were treated with FG-3019 for 45 weeks.
 - 38% showed either improved or stable lung fibrosis as measured by high-resolution CT scan.

There are currently many agents in mid-stage development for idiopathic pulmonary fibrosis (IPF)

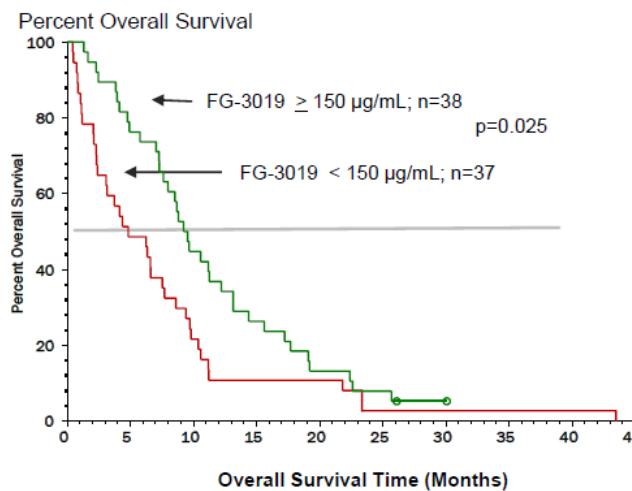
Drug	Company	Target	Phase
Esbriet (pirfenidone)	Roche (InterMune)	P38 MAPK, TGF β , TNF α	Approved
Ofev (nintedanib)	Boehringer Ingelheim	Tyrosine kinase	Approved
FG-3019	FibroGen	CTGF	II
simtuzumab	GILD	lysyl oxidase-like-2 (LOXL2)	II
QAX-576	NVS	IL13	II
lebrikizumab	Roche/Chugai	IL13	II
tralokinumab	AZN	IL13	II
SAR156597	SNY	IL4/13 (bispecific antibody)	I/II
TD139	Galecto Biotech	galectin-3	I/II
BMS-986020	BMY	Lysophosphatidic acid receptor 1 (LPA1)	II
STX-100	BIIB	Integrin alpha-V beta-6	II

FG-3019 produced dose-related increases in survival in pancreatic cancer

Relationship of 1-Year Survival to Dose



Relationship of Survival to FG-3019 Day-15 Plasma Levels



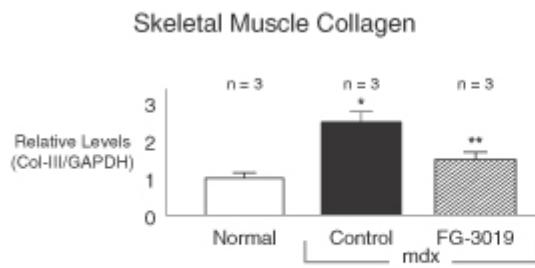
FG-3019 Day 15 C _{min}	n	Median OS (Months)	1-Year OS Rate
\geq median (150 $\mu\text{g/mL}$)	38	9.4	37%
<median (150 $\mu\text{g/mL}$)	37	4.8	11%
		0.0255 Log Rank Test	0.0137 Fisher's
		Hazard Ratio (95% CI)	1.73 (1.07 – 2.81)

Best Overall RECIST Response	n	(%)
Complete Response	2	(2.7)
Partial Response	8	(10.7)
Stable Disease	33	(44.0)
Progressive Disease	18	(24.0)
Not Done	14	(18.7)

- In dose-ranging study, FG-3019 was given in combination with gemcitabine and erlotinib
 - Patients with FG-3019 plasma levels of 150 $\mu\text{g/mL}$ or greater had improved survival compared those with less than 150 $\mu\text{g/mL}$
 - However, there were no significant differences in RECIST response rates between patients with high vs. low FG-3019 exposure or between patients with high vs. low baseline CTGF levels.

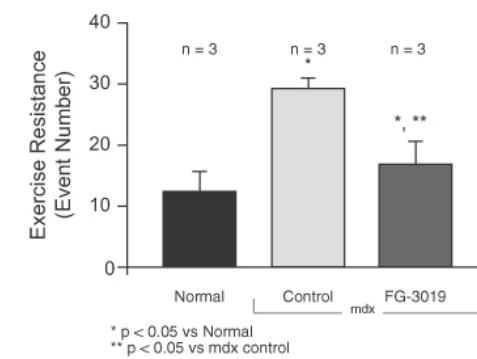
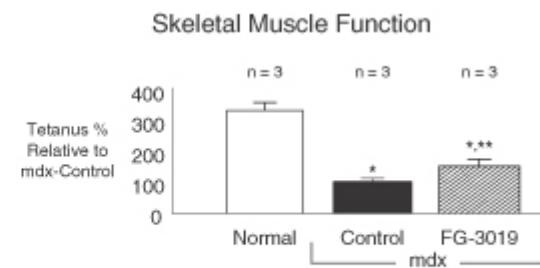
FG-3109 has been shown to decrease fibrosis in Duchenne Muscular Dystrophy (DMD)

- Higher levels of CTGF correlate with skeletal muscle fibrosis and precede the onset of cardiac dysfunction.
- In mouse models of DMD, FG-3109 was shown to decrease fibrosis, increase muscle strength, and improve exercise tolerance:



* p < 0.05 vs Normal
** p < 0.05 vs mdx control

Morales et al. Human Molecular Genetics, 2013, Vol. 22, No. 24



* p < 0.05 vs Normal
** p < 0.05 vs mdx control

- FibroGen plans to conduct a clinical trial with FG-3019 in DMD patients:
 - Will assess muscle pathology and function
 - Working with TREAT-NMD Advisory Committee for Therapeutics to design trial
 - Expects to initiate Phase II trial in DMD 2015

Other CTGF agents in development

Drug	Company	Indication	Phase
FG-3019	FibroGen	IPF	II
		Pancreatic cancer	III
		Liver Fibrosis	II
		DMD	II*
		Radiation counter measures	II*
PF-0647381	PFE/ISIS	Wound healing	II
RXI-109	RXII/Ethicor	Wound healing	II
RXI-2019	RXII	Liver Failure/Cirrhosis	Preclinical

*Trials expected to start in 2015

rhCollagen III Scaffold (FG-5200)

FG-5200 – Biosynthetic Cornea addresses worldwide shortage of donor corneas

- Used to treat corneal blindness (visual acuity of 3/60 or less) caused by trauma or disease
 - Worldwide annual incidence of 1.5-2.0M cases, accounting for 5.1% of all blindness's
 - Current treatments include:
 - Deceased-donor cornea transplant
 - 2-year success rates in developed countries ~85%, developing countries ~69%
 - 5- and 10-year success rates are 73% and 62%, respectively, according to the Australian Corneal Graft Registry
 - Current shortage and lack of tissue banking infrastructure limit the availability of donor corneas ex-US
 - Extraction of eye
 - Closing of eye with placental tissue
- FG-5200 is a cell-free implant comprising carbodiimide cross-linked recombinant human collagen (RHC)
 - Enables corneal regeneration by endogenous cell recruitment
 - Unlike donor cornea transplants, does not require long-term immunosuppression
- FibroGen plans to develop FG-5200 in China
 - Company estimates a built-up demand of over 1M patients, with an additional 200K new patients per year
 - Current supply of less than 4,000 donor corneas per year
 - Trial in China expected to be ~6 months long, have less than 100 patients
 - China has agreed to regulate as a Class III medical device
 - Company expects FG-5200 to qualify for "Green Pass" expedited approval

FG-5200 – Clinical Data

- 10-patient trial in Sweden with 4-year follow-up:
 - 4-year average corrected visual acuity of 20/54
 - Gain of more than 5 Snellen lines on an eye chart.
 - Regeneration evidenced by continued nerve and stromal cell repopulation
 - No inflammation or need for long-term immunosuppression
 - No recruitment of inflammatory dendritic cells into the implant area (see chart below)
 - No rejections seen

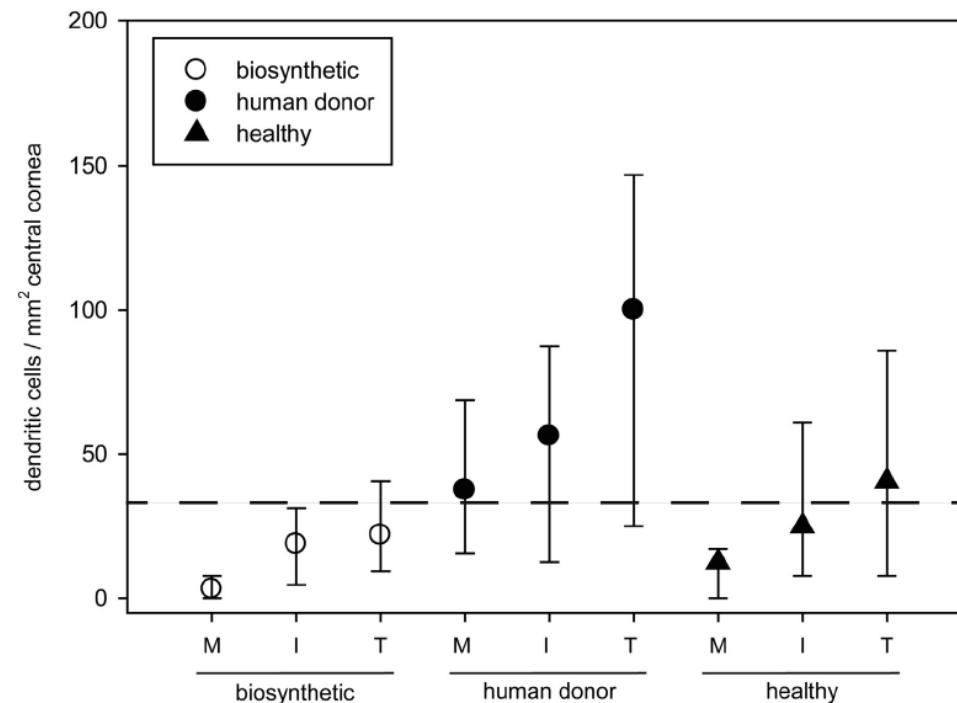


Fig. 3. *In vivo* confocal microscopic images of inflammatory dendritic cells at four years post-operation in regenerated neo-corneas compared to donor cornea grafted and normal, healthy eyes. (A) Few immature dendritic cells (white arrows) are seen in the basal epithelium of a regenerated neo-cornea. (B) Mature (black arrows) and immature (white arrows) dendritic cells in the central basal epithelial region of a cornea grafted with donor tissue, localized to the subbasal nerve plexus. (C) Mature (black arrow) and immature (white arrow) dendritic cells in the normal corneal basal epithelium. Scale bars, 100 µm. (D) Density of dendritic cells in the subbasal epithelium of the central cornea in healthy and 4 year post-operation groups. Data are given as median, 25th and 75th percentiles. M = mature dendritic cells (cell bodies with dendrites), I = immature dendritic cells (cell bodies only), T = total dendritic cells (mature + immature). The dashed line indicates the previously reported mean value of 34 ± 3 cells/mm² for the central corneal dendritic cell density in healthy eyes [16].

Financials, Intellectual Properties and Management

Key Financials

- 8.1M shares offered at the time of IPO –\$145.8M
- Cash, cash equivalents and investments (9/30/14)- \$308M (adjusted to include IPO proceeds)
- FibroGen is responsible for 50% of roxadustat development and commercialization costs in China, but ex-China costs are capped at \$116.5M.
- As of June 30, 2014, FibroGen has received upfront and other non-contingent milestone payments of \$360.1M and \$402.2M from Astellas and AZN, respectively. The company is eligible to receive developmental, regulatory, and commercial-based milestone payments totaling \$557.7M and \$1.22B from Astellas and AZN, respectively.
- Roxadustat program expected to be fully funded through launch from upfront, non-contingent and milestone payments, and development cost reimbursement
- AZN purchased \$20M of FibroGen common stock at the IPO price.

Partnerships and Terms

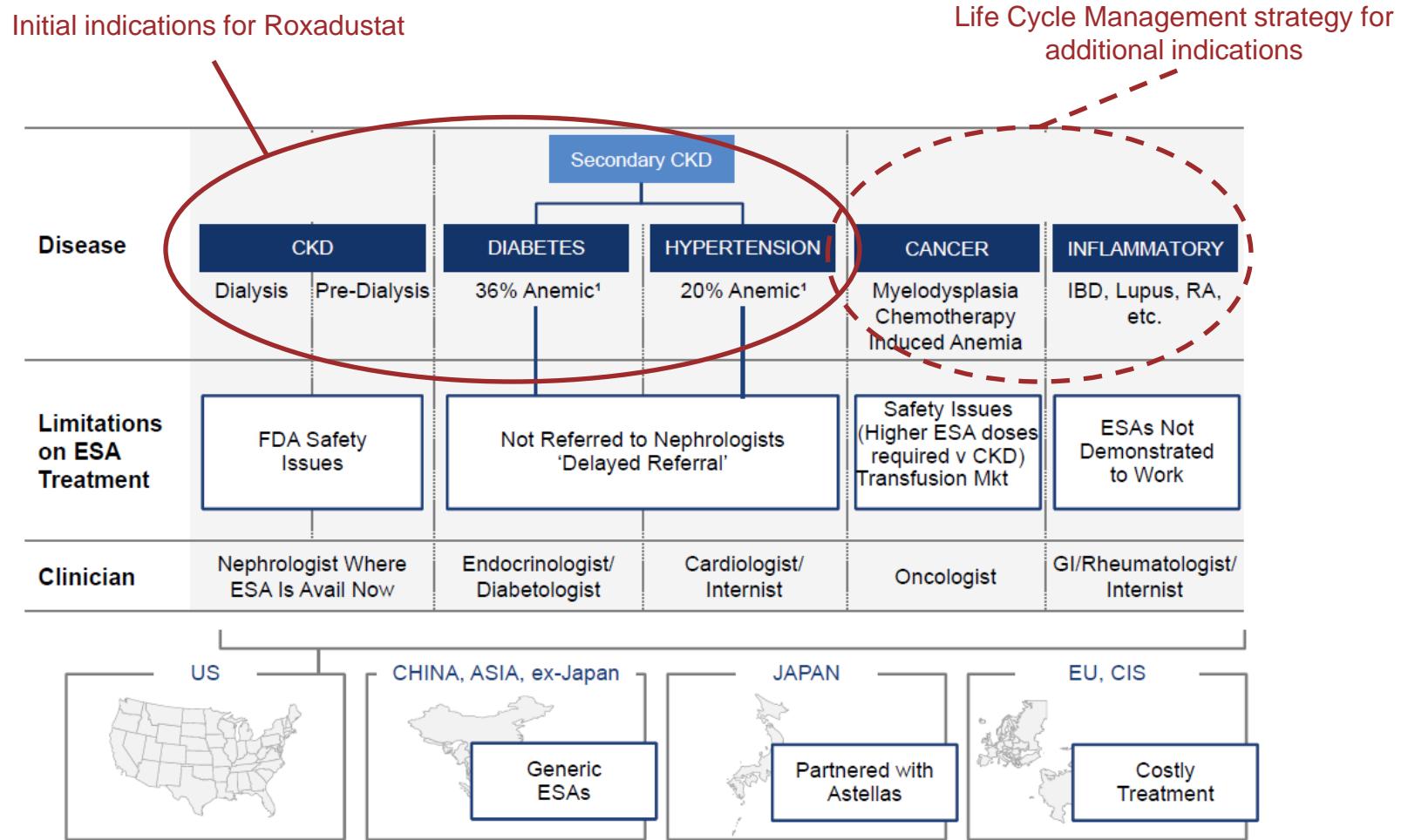
- Astellas Europe
 - Territory includes Europe, former Soviet Union, Middle East, and South Africa
 - 50/50 cost-share for US and EU development expenses (AZN responsible for FibroGen's share)
 - Astellas has EU regulatory responsibility, FibroGen has US responsibility
 - Astellas covers 100% of commercialization costs
 - FibroGen receives transfer price in the low 20% range and bears manufacturing costs
- Astellas Japan
 - Astellas covers 100% of development and commercialization costs and has regulatory responsibility
 - FibroGen receives transfer price in the low 20% range and bears manufacturing costs
- AZN US/ROW
 - Territory includes US and all non-Astellas territories
 - AZN pays 100% of development costs, other than those reimbursed by Astellas and \$116.5M paid by FibroGen
 - FibroGen receives a transfer price and royalties in the low-to-mid 20% range
- AZN China
 - 50/50 cost share for development costs and Beijing facility capital costs
 - Commercialization costs shared 50/50 (AZN advances launch costs)
- Upfront and milestone payments:

	PAYMENTS TO FIBROGEN	Cash Received Through June 30, 2014 (in millions)	Additional Potential	Total Potential
			Cash Payments Under Agreements	Cash Payments Under Agreements
	Upfront, Non Contingent	\$360.1	-	\$360.1
	Development & Reg Milestones	102.5	440.0	542.5
	Commercial Milestones	-	15.0	15.0
	Total Astellas	462.6	455.0	917.6
	Astellas Equity Investment	80.5	-	80.5
	Upfront, Non Contingent	220.2	182.0	402.2 ¹
	Development & Reg Milestones	-	571.0	571.0
	Commercial Milestones	-	652.5	652.5
	Total AstraZeneca	220.2	1,405.5	1,625.7
	AstraZeneca Equity Investment	-	20.0	20.0 [*]
	Total	\$763.3	\$1,880.5	\$2,643.8

Roxadustat IP

- Worldwide patent estate:
 - US Patents (3 granted, 1 pending for composition of matter, pharmaceutical compositions, and methods for treating anemia)
 - Composition-of-matter patents provide exclusivity through 2024 or 2025 (company expects 5 year Hatch-Waxman extension to 2029 or 2030)
 - Additional granted patents to expire between 2024 and 2027
 - Pending patent applications could extend protection to 2032 to 2034
 - Crystalline forms patent has been allowed by US PTO, expected to issue with patent term to 2033 (without extension)
 - European Patents
 - Granted and pending patents extend protection through 2024, and potentially beyond with regulatory exclusivity
 - China Patents
 - Granted patents protect through 2022 to 2024
 - 15 pending patents could extend to between 2022 and 2033
 - Extensive WW portfolio relating to treatment of anemia includes 45 granted patents and 65 pending applications
 - FibroGen is not aware of any 3rd-party patents or applications that would restrict freedom-to-operate

Anemia Market



- FibroGen expects to discuss life cycle management strategy with collaboration partners in 2H:14/1H:15
- Possibilities for next indications include oncology and anemia of inflammation

Ex-China, FibroGen has no commercialization costs and development costs are capped at \$116.5M

Astellas Partnership – EU, Japan, CIS, Middle East, and South Africa

Astellas
Product Revenue:
• Astellas books sales
Manufacturing, Supply:
• Bulk DP supplied by FibroGen
• Astellas COGS:
• Royalty/transfer price (low 20's) paid to FibroGen as % of net product sales
• Packaging and finishing by Astellas
Sales & Marketing:
• Astellas pays 100%
Product G&A
• Astellas pays 100%
R&D
• AZ and Astellas collectively pay 100%



FibroGen
Revenue:
• Royalty/Transfer price paid by Astellas
FibroGen COGS:
• Low single digit % of net product sales
Operational Expenses:
• Minimal non-billable expenses

AZN Partnership – US and ROW

AstraZeneca
Product Revenue:
• AZ books sales
Manufacturing, Supply:
• Bulk DP supplied by FibroGen
• AZ COGS:
• Royalty (low 20's) and transfer price (mid single digit) paid to FibroGen as % of net product sales
• Packaging and finishing by AZ
Sales & Marketing:
• AZ pays 100%, including FibroGen costs under US Co-Commercialization
Product G&A
• AZ pays 100%
• FibroGen Minimal OpEx
R&D
• AZ and Astellas collectively pay 100%



FibroGen
Revenue:
• Royalty paid by AZ
• Transfer price paid by AZ
FibroGen COGS:
• =< Transfer price paid by AZ
Operational Expenses:
• Generally reimbursed by AZ
• Minimal non-billable expenses

- AZN Partnership – China:
 - 50/50 profit share
 - Development and Commercialization costs are split 50/50
 - AZN responsible for Promotion and Marketing
 - FibroGen responsible for a portion of medical affairs efforts

Management

• Thomas B. Neff, Chairman, Founder, Chief Executive Officer

- Thomas Neff was employed as an investment banker first at Paine Webber Incorporated (1983-1988) and then at Lazard Freres & Co. through 1992. Mr. Neff was founder of Pharmaceutical Partners I and Pharmaceutical Partners II, the pioneer entities investing in drug royalties and predecessors to what is now Royalty Pharma. He was also founder and General Partner of Three Arch Bay Health Science Fund, a private investment fund focused on emerging biomedical companies, from 1993 to completion in 2011. He received an honorary doctor of medical sciences from Oulu University, Oulu, Finland in 2009. He has been a director of Kolttan Pharmaceuticals, a spin-out from Yale University, since 2009. Mr. Neff is a named inventor on over 100 of FibroGen's patents and patent applications. Mr. Neff received a B.A. from Claremont McKenna College with concentrations in Molecular Biology and Government. Subsequently he studied Economics and Finance at the University of the Chicago Graduate School of Business, and was a Fellow of the Thomas J Watson Foundation.

• Pat Cotroneo, Vice President, Finance, and Chief Financial Officer

- Pat Cotroneo has served as FibroGen's CFO since 2008. Mr. Cotroneo joined the company in 2000 as Controller, was promoted to Vice President of Finance, and subsequently promoted to Chief Financial Officer in 2008. Prior to joining FibroGen, Mr. Cotroneo was at SyStemix, Inc. where he assumed Controller responsibilities for both SyStemix and Genetic Therapy, Inc. (Novartis subsidiaries) from 1993 to 2000. Prior to SyStemix, he was employed by Deloitte & Touche from 1987 to 1993 in various positions. Mr. Cotroneo received a B.S. with honors from the University of San Francisco and was selected a Louise M. Davies scholar.

• Frank H. Valone, M.D., Chief Medical Officer

- Frank Valone, M.D., has served as FibroGen's Chief Medical Officer since December 2008. Dr. Valone has more than 14 years of biotechnology industry experience in the leadership of clinical and preclinical development, medical and regulatory affairs and quality assurance and control. He served as Senior Vice President of Medical Affairs of Bayhill Therapeutics Inc. from November 2003 to November 2008. Dr. Valone served as Executive Vice President of Clinical Development and Regulatory Affairs of Titan Pharmaceuticals Inc. from March 2002 to October 2003. From 1994 to 2002, Dr. Valone was the Chief Medical Officer and Senior Vice President of Clinical and Regulatory Affairs of Dendreon Corporation. From 1991 to 1996, he served in various positions of The Dartmouth-Hitchcock Medical Center as Adjunct Professor of Medicine and Norris Cotton Cancer Center including Professor of Medicine. From 1982 to 1991, Dr. Valone held various positions at The University of California, San Francisco, including Associate and Chief of Hematology and Oncology at the San Francisco VA Medical Center. From 1995 to 2001, he was Clinical Associate Professor, Department of Medicine, Stanford University. Dr. Valone received a B.A. from Hamilton College and an M.D. from Harvard Medical School. His Post-Doctoral training was at the Brigham and Women's Hospital in Internal Medicine/Allergy and Rheumatology and at Dana-Farber Cancer Institute in Medical Oncology in 1980.

• K. Peony Yu, M.D., Vice President, Clinical Development

- K. Peony Yu, M.D, has served as FibroGen's Vice President of Clinical Development since December 2008. Prior to joining the company, Dr. Yu was Vice President of Clinical Research at Anesiva, Inc. Prior to Anesiva, Dr. Yu was Director, Clinical Development, at ALZA Corporation (a subsidiary of Johnson & Johnson) where she was Global Clinical Lead for IONSYS, a drug-device combination for post-operative pain. Prior to ALZA, Dr. Yu held previous posts at Pain Therapeutics, Inc., and at Elan Pharmaceuticals. Dr. Yu received a B.S. in Chemical Engineering and an M.D. both from the University of California, Davis, followed by residency training at Stanford Medical School.

FGEN P&L Model, \$M except per share data	2011A	2012A	2013A	Q1:14A	Q2:14A	Q3:14A	Q4:14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
	2011A	2012A	2013A					2014E	2015E	2016E	2017E	2018E	2019E	2020E
AZN partnership														
US Sales (POS-adj.)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	144.2	329.6
ROW Sales (POS-adj.)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	43.3	98.9
Total AZN royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	44.0	100.7
China Sales (POS-adj.)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	56.9	124.2	212.4
Astellas partnership														
EU Sales (POS-adj.)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	115.3	263.6
Japan Sales (POS-adj.)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	57.7	131.8
Total Astellas Royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	34.6	79.1
Total roxadustat sales/royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	56.9	202.9	392.2
License/milestone revenues	1.2	62.8	95.0	48.6	48.6	9.0	15.0	121.2	182.0	155.0	10.5	63.7	259.9	259.9
Collaboration services and other revenue	12.6	3.1	7.2	5.4	5.4	4.6	5.0	20.3	20.0	20.0	20.0	20.0	20.0	20.0
Total revenue	13.8	65.9	102.2	53.9	53.9	13.6	20.0	141.5	202.0	175.0	30.5	140.6	482.8	672.1
R&D	65.4	74.2	85.7	29.5	29.5	40.6	50.0	149.5	205.0	150.0	160.0	170.0	180.0	190.0
SG&A	23.8	18.9	24.4	7.0	7.0	10.2	11.0	35.1	45.0	60.0	62.0	64.0	66.0	68.0
Profit share payment to AZN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	28.5	62.1	106.2
Total operating expense	89.2	93.2	110.1	36.4	36.4	50.8	61.0	184.6	250.0	210.0	222.0	262.5	308.1	364.2
Operating income	(75.4)	(27.2)	(7.9)	17.5	17.5	(37.2)	(41.0)	(43.1)	(48.0)	(35.0)	(191.5)	(121.9)	174.7	307.9
Interest expense and other, net														
Interest expense	(10.0)	(10.7)	(2.7)	(2.7)	(2.7)	(2.7)	(2.7)	(10.9)	(10.9)	(10.9)	(10.9)	(10.9)	(10.9)	(10.9)
Interest income	4.4	3.6	0.9	0.9	(0.5)	0.0	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Other income (expense), net	0.2	0.2	0.1	0.1	(0.2)	0.0	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Total interest and other, net	(5.4)	(7.0)	(1.7)	(1.7)	(3.4)	(2.7)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)
Income (loss) before income taxes	(32.7)	(14.9)	15.8	15.8	(40.5)	(43.7)	(52.7)	(57.5)	(44.5)	(201.0)	(131.4)	165.2	298.4	
Benefit from income taxes	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net income (loss)	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EPS (basic)														
EPS (diluted)	(\$0.69)	(\$0.32)	\$0.33	\$0.33	(\$0.86)	(\$0.77)	(\$1.06)	(\$1.00)	(\$0.77)	(\$3.44)	(\$2.23)	\$2.77	\$4.95	
Shares - basic (pro-forma)	47.106	47.106	47.106	47.275	47.275	47.275	56.737	49.640	57.304	57.877	58.456	59.041	59.631	60.227
Shares - diluted (pro-forma)	60.249	60.249	60.249	60.418	60.418	60.418	70.839	63.024	71.548	72.263	72.986	73.716	74.453	75.197

Source: Company filings, Leerink estimates

Disclosures Appendix**Analyst Certification**

I, Howard Liang, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 09/30/14
**IB Serv./Past 12
Mos.**

Rating	Count	Percent	<hr/>	
			Count	Percent
BUY [OP]	138	69.30	51	37.00
HOLD [MP]	61	30.70	2	3.30
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months. The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than \$2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over \$2 billion.

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