FIBROGEN INC
Form 10-K
March 26, 2015
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2014

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____.

Commission file number: 001-36740

FIBROGEN, INC.

(Exact name of registrant as specified in its charter)

Delaware	**77-0357827**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
409 Illinois Street	
San Francisco, CA	**94158**
(Address of principal executive offices)	**(zip code)**

Registrant s telephone number, including area code:

(415) 978-1200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Exchange on Which Registered**
Common Stock, $0.01 par value	**The NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ¨ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act:

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer x (Do not check if a smaller reporting company)	Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). Yes ¨ No x

As of June 30, 2014, the last business day of the registrant s most recently completed second fiscal quarter, there was no established public market for the registrant s common stock. The registrant s common stock began trading on The NASDAQ Global Select Market on November 14, 2014.

The number of shares of common stock outstanding as of February 28, 2015 was 59,137,591.

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FORWARD-LOOKING STATEMENTS

This Annual Report filed on Form 10-K and the information incorporated herein by reference, particularly in the sections captioned Risk Factors, Management s Discussion and Analysis of Financial Condition and Results of Operations and Business, contains forward-looking statements, which involve substantial risks and uncertainties. In this Annual Report, all statements other than statements of historical or present facts contained in this Annual Report, including statements regarding our future financial condition, business strategy and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as believe, will, may, estimate, continue, anticipate, contemplate, intend, target, project, should, plan, expect, predict, could, potentially or the negative of these terms or other similar terms or expressions that concern our expectations, strategy, plans or intentions. Forward-looking statements appear in a number of places throughout this Annual Report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for roxadustat, FG-3019 and our other product candidates, our intellectual property position, the potential safety, efficacy, reimbursement, convenience clinical and pharmaco-economic benefits of our product candidates, the potential markets for any of our product candidates, our ability to develop commercial functions, our ability to operate in China, expectations regarding clinical trial data, our results of operations, cash needs, spending of the proceeds from our initial public offering and the concurrent private placement, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in the section of this Annual Report captioned Risk Factors and elsewhere in this Annual Report.

These risks are not exhaustive. Other sections of this Annual Report may include additional factors that could adversely impact our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. We cannot assure you that the events and circumstances reflected in the forward-looking statements will be achieved or occur. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. The forward-looking statements made in this Annual Report are based on circumstances as of the date on which the statements are made. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report or to conform these statements to actual results or to changes in our expectations.

This Annual Report also contains market data, research, industry forecasts and other similar information obtained from or based on industry reports and publications, including information concerning our industry, our business, and the potential markets for our product candidates, including data regarding the estimated size and patient populations of those and related markets, their projected growth rates and the incidence of certain medical conditions, as well as physician and patient practices within the related markets. Such data and information involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates.

You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and achievements may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

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ITEM 1. BUSINESS

OVERVIEW

We are a research-based, biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutic agents to treat serious unmet medical needs. We have capitalized on our extensive experience in fibrosis and hypoxia inducible factor, or HIF, biology to generate multiple programs targeting various therapeutic areas. Our most advanced product candidate, roxadustat, or FG-4592, is an oral small molecule inhibitor of HIF prolyl hydroxylases, or HIF-PHs, in Phase 3 clinical development for the treatment of anemia in chronic kidney disease, or CKD. Our second product candidate, FG-3019, is a monoclonal antibody in Phase 2 clinical development for the treatment of idiopathic pulmonary fibrosis, or IPF, pancreatic cancer and liver fibrosis. We have taken a global approach to the development and future commercialization of our product candidates, and this includes development and commercialization in the People s Republic of China, or China.

We intend to leverage our extensive experience in fibrosis and HIF biology to build a successful biopharmaceutical company with a strong pipeline of products and product candidates for the treatment of anemia, fibrosis, cancer, corneal blindness and other serious unmet medical needs. The chart below is a summary of our most advanced product candidates:

ROXADUSTAT FOR THE TREATMENT OF ANEMIA IN CHRONIC KIDNEY DISEASE

Roxadustat is an internally discovered HIF-PH inhibitor that acts by stimulating the body s natural pathway of erythropoiesis, or red blood cell production. Roxadustat, the first HIF-PH inhibitor to enter Phase 3 clinical development, represents a new paradigm for the treatment of anemia in CKD patients, with the potential to offer a safer, more effective, more convenient and more accessible therapy than the current therapies available for anemia in CKD, such as injectable erythropoiesis stimulating agents, or ESAs.

Roxadustat is currently in Phase 3 global development for the treatment of anemia in patients with chronic kidney disease, or CKD. Over 1,400 subjects have participated in 26 completed Phase 1 and 2 clinical studies for

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roxadustat in North America, Europe and Asia. These studies have demonstrated roxadustat s potential for a favorable safety and efficacy profile in anemic CKD patients, both those who are dialysis-dependent, or DD-CKD, including hyporesponsive patients, and those who are not dialysis-dependent, or NDD-CKD. According to IMS Health, 2013 global ESA sales in all anemia indications totaled $8.6 billion. While the use of ESAs to treat anemia in CKD has largely been limited to use in DD-CKD patients, we and our partners believe that, as an oral agent with a potentially more favorable safety profile, roxadustat could increase accessibility and expand the market for anemia treatment by penetrating the NDD-CKD market. In the longer term, we believe roxadustat has the potential to address non-CKD anemia markets, including chemotherapy-induced anemia, anemia related to inflammation (such as inflammatory bowel disease, lupus and rheumatoid arthritis), myelodysplastic syndrome, or MDS, and surgical procedures requiring transfusions.

We, along with our collaboration partners Astellas Pharma Inc., or Astellas, and AstraZeneca AB, or Astra Zeneca, have designed a global Phase 3 program to support regulatory approval of roxadustat in both NDD-CKD and DD-CKD patients in the United States, the European Union, Japan and China. Our US and EU Phase 3 program has an aggregate target enrollment of approximately 7,000 to 8,000 patients worldwide and is the largest Phase 3 clinical program ever conducted for an anemia product candidate. Our Phase 3 program is also designed and sized for, and will incorporate major adverse cardiac events, or MACE, composite safety endpoints that we believe will be required for approval in the United States for all new anemia therapies. Our Phase 3 program will study multiple patient populations, including patients within the first four months of initiating dialysis, or incident dialysis, and non-incident, or stable, dialysis patients and will include multiple NDD-CKD studies comparing roxadustat against placebo control.

Background of Anemia in CKD

Anemia is a serious medical condition in which patients have insufficient red blood cells and low levels of hemoglobin, or Hb, a protein in red blood cells that carries oxygen to cells throughout the body. Anemia is associated with increased risks of hospitalization, cardiovascular complications, need for blood transfusion, exacerbation of other serious medical conditions and death. In addition, anemia frequently leads to significant fatigue, cognitive dysfunction, and decreased quality of life. The more severe the anemia, as measured in lower Hb levels, the greater the health impact on patients. Severe anemia is common in patients with CKD, cancer, MDS, inflammatory diseases, and other serious illnesses. Even when it accompanies prevalent and serious diseases, anemia is often not effectively treated.

Anemia is particularly prevalent in patients with CKD, which is a critical healthcare problem and is most commonly caused by diabetes and hypertension in the United States and Europe. CKD affects over 200 million people worldwide and anemia significantly increases healthcare costs for those patients. CKD is generally a progressive disease characterized by the gradual loss of kidney function that may eventually lead to kidney failure, also known as end stage renal disease, or ESRD. Patients with ESRD require renal replacement therapy either dialysis treatment or kidney transplantation. CKD accompanied by anemia is associated with worse health outcomes than CKD alone, including more rapid progression of CKD and increased death rate. There are 5 stages of CKD which are primarily defined by a measure of the filtration function of the kidney (GFR).

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Stages of CKD and Prevalence in the United States

* US prevalence is estimated for adults 20 years of age or older
GFR: Glomerular Filtration Rate (ml/min/1.73m^2)
Sources: The prevalence of stage 1 through stage 4 CKD was calculated based on 2012 estimates by the U.S. Renal Data System (USRDS) using data from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 and 2012 data from the U.S. Census Bureau. The prevalence of stage 5 CKD was calculated based on 2012 data from the USRDS using data from NHANES 2007-2012 and 2012 data from the U.S. Census Bureau.

The prevalence rate of anemia in patients with Hb<12 g/dL is set forth below.

Sources: The prevalence of anemia in stage 1 through stage 4 CKD and stage 5 NDD-CKD were derived from Stauffer and Fan, Prevalence of Anemia in Chronic Kidney Disease in the United States, PLoS ONE (2014). The prevalence of anemia in patients undergoing dialysis was derived from Goodkin et al, Naturally Occurring Higher Hemoglobin Concentration Does Not Increase Mortality among Hemodialysis Patients, J Am Soc Nephrol (2011).

In the United States, according to the USRDS, a majority of dialysis eligible CKD patients are currently on dialysis. According to USRDS data as of 2012, approximately 450,000 patients were receiving dialysis in the United States, of whom approximately 80% were being treated with ESAs for anemia. Despite the presence of anemia in stages 3 and 4 CKD patients, in clinical practice, patients typically do not receive ESA treatment for their anemia until they initiate dialysis. Approximately 15% of U.S. NDD-CKD patients were being treated with ESAs prior to initiation of dialysis as of 2012 (USRDS Annual Data Report (2014)). In many CKD patients, the disease progresses gradually over decades and, therefore, patients can spend years suffering from the symptoms and negative health impacts of anemia before they receive treatment. Many of these patients die from cardiovascular events before they initiate dialysis.

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Limitations of the Current Standard of Care for Anemia in CKD

Current therapies to treat anemia in CKD include injectable ESAs, intravenous iron, or IV iron, oral iron and blood transfusions. ESAs have been used in the treatment of anemia in CKD for over 20 years and are administered intravenously or subcutaneously, typically in conjunction with IV iron. NDD-CKD patients who are not under the care of nephrologists, including those with diabetes and hypertension, do not typically receive ESAs and are often left untreated. ESAs currently on the market are all synthetic recombinant versions of human erythropoietin, or EPO, a hormone that stimulates erythropoiesis and increases Hb levels by binding to receptors on red blood cell precursors in the bone marrow.

The introduction of the first ESA in 1989 was viewed as a major advance in the treatment of anemia in CKD because it significantly decreased the need for blood transfusions. Since then, ESAs have become one of the most commercially successful drug classes. However, because ESAs were never studied relative to placebo in large randomized clinical trials prior to approval, it was not until years later that their safety profile became better elucidated. Studies published in 2006 to 2009 demonstrated the safety risks of higher ESA doses used to target Hb levels of 13 to 15 g/dL, prompting physicians to balance serious safety concerns against the efficacy of ESAs. The safety concerns observed with injectable ESAs in these studies included an increased risk of cardiovascular adverse events and death as well as a potentially increased rate of tumor recurrence in patients with cancer.

The emergence of the safety issues resulted in several changes to ESA drug labeling. This combination of safety concerns and labeling changes, in addition to the subsequent reimbursement changes, described below, was followed by a decline in ESA sales revenues beginning in 2007. While we believe this decline in ESA sales is primarily due to complete suspension of the label for use of ESAs in anemias associated with cancer, and restrictions on use in chemotherapy induced anemia, we believe the decline in sales is also partly due to the progressive decline in ESA dose administered to CKD patients. Compared to the average ESA dose at the end of 2006, the mean monthly ESA dose in patients on hemodialysis dropped by 18%, 36% and 45% by the end of 2010, 2011 and 2012 respectively (USRDS Annual Data Report 2014).

Safety Issues of ESAs

Several large clinical trials were designed to demonstrate that targeting higher as opposed to lower Hb levels results in better outcomes. However, they instead generated data showing that targeting higher Hb levels with ESAs resulted in an increase in adverse events, including cardiovascular adverse events. These adverse events were initially observed in 1998 in the NHCT (Normal Hematocrit Cardiac Trial) in CKD patients on dialysis, where the high Hb level treatment arm targeted Hb levels of 13 to 15 g/dL. Additional safety concerns emerged following the CHOIR (Correction of Hemoglobin in Outcomes and Renal Insufficiency), CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta), and TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) studies in NDD-CKD patients, which were published between 2006 and 2009.

Secondary analyses of NHCT, CHOIR and TREAT, as well as subsequent observational studies in dialysis patients, suggest that these safety concerns, particularly the increased cardiovascular risk associated with ESAs, may result from the high ESA doses used to target higher Hb levels rather than the achieved Hb levels themselves. For example, a secondary analysis of CHOIR showed that patients who achieved the desired Hb level with the lowest amounts of ESA have the lowest risk of adverse cardiovascular outcomes as measured by composite endpoints consisting of hospitalization for heart failure, heart attack, stroke, and death. Patients who were treated with the highest ESA doses and, particularly those who achieved the lowest Hb levels, had the greatest risk for these events. In addition, observational studies in patients undergoing dialysis highlighted these risks with high ESA doses and also indicated that higher Hb levels achieved with lower ESA doses were associated with better outcomes.

For example, in an analysis of data from the USRDS of 94,569 hemodialysis patients, increased mortality was found in patients with increased epoetin alfa dose. Patients who achieved the highest hematocrit level (which is a

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measure of the percentage of volume of whole blood made up of red blood cells; under typical conditions, Hb level can be estimated as one-third the hematocrit level) and received the lowest ESA doses (lowest dose quartile, Q1) had the lowest mortality rate, and, at any particular ESA dose quartile, patients with higher hematocrit levels tended to have lower mortality levels, according to Zhang et al (Am J Kidney Dis 44:866-876) as illustrated in the chart below.

Unadjusted 1-Year Mortality Rates (per 1000)

by Hematocrit and ESA dosing quartile

Warnings about these risks have been incorporated into guidelines and position papers from major kidney societies and thought leaders. Kidney Disease: Improving Global Outcomes, or KDIGO, a non-profit foundation established in 2003 and operated by the National Kidney Foundation, committed to improving global clinical guidelines for kidney patients, for example, states that, [t]here may be toxicity from high doses of ESA, as suggested, though not proven, by recent post-hoc analyses of major ESA randomized controlled trials, especially in conjunction with the achievement of high Hb levels. Therefore, in general ESA dose escalation should be avoided. In addition, the European Renal Best Practices Group specified in a recent position statement that caution should be used in ESA therapy in patients with specific risk factors.

Limited Effectiveness of ESAs in Certain Patient Populations

Hb responses to ESA doses are on a continuum with some patients responding with a satisfactory Hb increase to a small ESA dose and others responding very poorly to very high doses. In addition, patients responsiveness to ESAs can change over time and as a result of circumstances such as acute illness or surgery. In an attempt to reach target Hb level, ESA doses are increased in treatment-resistant patients, or hyporesponders, which can result in up to a 40-fold difference in ESA doses between the most ESA-resistant and the most ESA-responsive DD-CKD patients. Even with high doses of ESAs and concomitant IV iron, some of these hyporesponders are unable to reach target Hb levels.

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Hyporesponsiveness is a significant problem in incident dialysis patients, for whom ESA doses are typically high, and is associated with a combination of critically low kidney function and accompanying illnesses, such as infections and chronic inflammation. Incident dialysis patients are generally more anemic, and have a higher risk of death, than patients who have been on dialysis for many months.

A major cause of ESA hyporesponsiveness is an underlying chronic inflammatory state that exists in many CKD patients. Chronic inflammation has a suppressive effect on erythropoiesis in CKD via two main mechanisms. Firstly, pro-inflammatory cytokines such as tumor necrosis factor alpha, or TNF-alpha, and interleukin-6, or IL-6, have been implicated in the suppression of erythropoiesis through inhibition of the response of erythroid progenitor cells to EPO. Secondly, pro-inflammatory cytokines such as IL-6 elevate the levels of hepcidin, the major hormone that regulates iron metabolism. The consequence of elevated hepcidin levels is a reduction in iron absorption from the gastrointestinal tract, or GI tract, and the trapping of iron in cellular stores. Together this leads to inadequate availability of iron to keep pace with the demands of the bone marrow for erythropoiesis, despite adequate total body iron stores. This condition is referred to as functional iron deficiency.

In the presence of inflammation, even high doses of ESAs may be ineffective to achieve target Hb levels, and to the extent Hb levels are raised, the risks associated with the higher ESA doses required may outweigh the benefits of any increased Hb levels.

Requirement for IV Iron to Support ESA Activity and Associated Safety Risks

IV iron supplementation is used to support anemia correction in a majority of hemodialysis patients treated with ESAs in the United States. ESA labeling indicates that physicians should evaluate the iron status in all patients before and during CKD anemia treatment and maintain iron repletion. Many CKD patients have deficient iron stores, or absolute iron deficiency, and cannot absorb enough iron from diet or oral iron supplements to correct this deficiency. Physicians administer IV iron to ensure patients are iron replete prior to initiating ESA treatment and continue IV iron to mitigate iron depletion caused by ESA-mediated erythropoiesis.

Additionally, many CKD patients who have adequate iron stores suffer from functional iron deficiency. IV iron is administered in an attempt to address this shortage of available iron in these CKD patients, resulting in many patients having elevated body iron stores. While IV iron can help correct anemia when used with ESAs, published studies have suggested acute and chronic risks of both morbidity and mortality associated with the use of IV iron. The acute risks of IV iron supplementation include hypersensitivity reactions (which can be life-threatening and the warning of anaphylaxis risk appears in every IV iron product package insert in the United States), infection, as well as less severe but more common side-effects, such as skin problems, hypotension and GI tract symptoms. In addition to acute side-effects, there may also be chronic adverse effects on organ systems related to the cumulative deposits of iron resulting from the volume of iron administered.

Increased use of IV iron has been associated with increased risk of hospitalization and death. Using data from 12 countries obtained over the past twelve years, Bailie et al. demonstrated a direct dose risk relationship between the amount of IV iron administered per month to dialysis patients and the risk of hospitalization and death (Kidney International (2014)). The study identified that, even after controlling for other risk factors and adjusting for different practice patterns globally, dialysis patients receiving greater than 300 mg of IV iron per month had a greater risk of hospitalization or death than those receiving less than 300 mg. Mortality was 13% greater among those receiving between 300 and 400 mg of IV iron per month and 18% greater among those receiving greater than 400 mg of IV iron per month. Furthermore, hospitalization risk was 12% greater among those who received greater than 300 mg per month. The current paradigm of administrating greater doses of IV iron to decrease ESA doses in light of this recently described associated risk underscores the significant unmet need in the treatment of anemia. However, new and

purportedly safer and more effective iron supplementation therapies are being developed and introduced, and if such new therapies are accepted by patients and physicians as a superior alternative to traditional IV iron supplementation therapies, they may help maintain or increase the attractiveness of ESA therapy.

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Elevated Blood Pressure

ESAs have long been associated with increased blood pressure, including new onset hypertension and exacerbation of pre-existing hypertension. As a result, ESA labeling carries a warning for the potential for increased blood pressure with ESA usage. Hypertension has been shown to accelerate CKD progression and significantly increase the risk of death in CKD patients due to the increased risk of heart attack or stroke.

Increased Thromboembolism and Vascular Access Thrombosis

ESA use has been associated with thromboembolic events, including stroke, vascular access thrombosis (where the dialysis access shunt is blocked due to blood-clotting), blood clots in the leg, which may in part be due to increases in circulating platelet levels. As a result, ESA labeling carries a warning for an increased risk of thromboembolic events.

FDA Restrictions on ESA Usage

In response to safety concerns elucidated in the large clinical studies described above, the US Food and Drug Administration, or the FDA, steadily increased restrictions on the use of injectable ESAs from 2007 through 2011. During 2007, following the NHCT, CHOIR and CREATE studies and several oncology studies, the FDA mandated the inclusion of a boxed warning, or Black Box warning, in the package insert for ESAs. A Black Box warning is the strongest warning that the FDA can require in the package insert of prescription drugs. In June 2011, the FDA required further modification to the package insert for ESAs. The current boxed warning states that ESAs increase the risk of death, myocardial infarction, or heart attack, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. In addition, the package insert changes include more conservative dosing guidelines for the use of injectable ESAs in anemic CKD patients. Specifically, the FDA removed the prior target Hb range of 10 to 12 g/dL and recommends that physicians initiate treatment of CKD patients when the Hb level is less than 10 g/dL and reduce or interrupt ESA dosing if the Hb level approaches or exceeds 10 g/dL for NDD-CKD patients and 11 g/dL for DD-CKD patients. In addition, physicians are advised to use only the lowest dose needed to avoid red blood cell transfusions.

Reimbursement Challenges Associated with ESAs

In addition to the safety concerns and labeling changes for ESAs, the reimbursement applicable to dialysis, including associated drugs such as ESAs, has also changed significantly in recent years, which made ESAs less economically attractive for providers to administer. Prior to January 2011, CMS reimbursed dialysis centers and other healthcare providers for use of ESAs at average selling price plus a premium to their cost, which enabled providers to realize a profit on the administration of ESAs, regardless of the quantity dosed. Under the Medicare Improvements for Patients and Providers Act, or MIPPA, a basic case-mix adjusted composite, or bundled, payment system commenced in January 2011 and transitioned fully by January 2014 to a single reimbursement rate for drugs and all services furnished by renal dialysis centers for Medicare beneficiaries with end-stage renal disease. Specifically, under MIPPA the bundle now covers drugs, services, lab tests and supplies under a single treatment base rate for reimbursement by CMS based on the average cost per treatment, including the cost of ESAs and IV iron doses, typically without adjustment for usage.

ESAs administered to NDD-CKD patients have long been reimbursed under Medicare Part B, which requires providers to purchase and store ESAs in advance of being reimbursed, and in many healthcare practices, the amount reimbursed does not cover the cost of ESA administration. For many of these providers, including in nephrology practices where purchase and storing is most common, due to label changes and related reduction in patients available for treatment, ESA administration in NDD-CKD has become economically unattractive. Furthermore,

non-nephrologists generally have elected not to provide ESAs. Accordingly, ESA treatment has been limited outside of dialysis centers.

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Inconvenience of ESAs

In addition to safety, labeling, reimbursement and efficacy limitations, ESAs must be administered intravenously or subcutaneously, often with IV iron in order for ESAs to be effective at treating to target Hb levels. ESAs are therefore inconvenient for the NDD-CKD population, the peritoneal dialysis population, for whom treatment is often administered at home, and other non-CKD anemia patients who are not already regularly visiting a hospital or dialysis center.

Our Solution

We believe that there is a significant need for a safer, more effective, more convenient and more accessible alternative to injectable ESAs for the treatment of anemia in CKD patients. In addition, we believe there is a significant opportunity for treatment of anemia in markets not effectively addressed by ESAs, such as in the NDD-CKD population, DD-CKD in the presence of inflammation, and non-CKD anemia markets.

Roxadustat A Novel, Orally Administered Treatment for Anemia

Roxadustat is an orally administered small molecule that corrects anemia by a different mechanism of action from that of ESAs. As a HIF-PH inhibitor, roxadustat activates a response that is naturally activated when the body responds to reduced oxygen levels in the blood, such as when a person adapts to high altitude. The response activated by roxadustat involves the regulation of multiple, complementary processes to promote erythropoiesis and increase the blood s oxygen carrying capacity. This coordinated erythropoietic response includes both the stimulation of red blood cell progenitors, by increasing the body s production of EPO, and an increase in iron availability for Hb synthesis. Patients taking roxadustat typically have circulating endogenous EPO levels at peak concentration within or near the physiologic range naturally experienced by people adapting to hypoxic conditions such as at high altitude, following blood donation or impaired lung function, such as pulmonary edema. By contrast, ESAs act only to stimulate red blood cell progenitors without a corresponding increase in iron availability, and are typically dosed at well above the natural physiologic range of EPO. The sudden demand for iron stimulated by ESA-induced erythropoiesis can lead to functional or absolute iron deficiency. We believe these high doses of ESAs are a main cause of the significant safety issues that have been attributed to this class of drugs. In contrast, the differentiated mechanism of action of roxadustat, which involves induction of the body s own natural pathways to achieve a more complete erythropoiesis, has the potential to provide a safer and more effective treatment of anemia, including in the presence of inflammation, which normally limits iron availability.

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Our HIF-PH inhibitor technology relies on the natural mechanism by which the body responds to low oxygen levels. HIF is a transcription factor comprised of a HIF-alpha and a HIF-beta subunit, both of which are required to stimulate erythropoiesis. Under normal oxygen conditions, the HIF-alpha subunit is targeted for rapid degradation through the activity of a family of HIF-PH enzymes. However, under low oxygen conditions, the HIF-PH enzymes cannot function and HIF-alpha accumulates. HIF-alpha then combines with HIF-beta, and the newly formed HIF complex initiates transcription of a number of genes involved in the erythropoietic process, which ultimately leads to increased oxygen delivery to tissues. Roxadustat works by reversibly inhibiting the HIF-PH enzymes, thus mimicking this coordinated natural erythropoietic response through genes transcribing the proteins shown below involved in iron absorption, mobilization and transport as well as stimulation of red blood cell progenitors.

Our discovery and development of roxadustat resulted from years of experience working with prolyl hydroxylase enzymes, such as those that regulate HIF, and a deep understanding of the complexities of HIF biology. We have explored therapeutic activation of HIF to treat anemia from an integrated perspective with a focus on applying our HIF-PH inhibitor technology to produce coordinated effects on erythropoiesis and iron homeostasis and metabolism. As part of these progressive efforts, we have explored the ability of our HIF-PH inhibitor technology to increase sensitivity to endogenous EPO by increasing EPO receptor expression on red blood cell progenitors. We have investigated multiple effects of HIF-PH inhibitors on iron metabolism, including their ability to regulate genes that can increase iron bioavailability. We have also shown that administration of HIF-PH inhibitors can decrease expression of hepcidin, the key hormone that regulates iron metabolism. Hepcidin is elevated under conditions of chronic inflammation, leading to reduced iron availability for erythropoiesis. Based on our gene expression and hepcidin data, we believe HIF-PH inhibitors can increase intestinal iron absorption and enhance the mobilization and uptake of iron. In addition, we have shown that HIF-PH inhibitors can improve

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transferrin saturation (a measure of circulating iron available for erythropoiesis) and can correct anemia associated with chronic inflammation by overcoming the hepcidin-mediated sequestration of iron that cannot be overcome by ESA therapy.

We selected roxadustat from our extensive library of compounds from various chemical classes of HIF-PH inhibitors, including heterocyclic carboxamides and 2-oxoglutarate mimetics. Roxadustat was selected based on our belief that stabilizing the two main forms of HIF in the cell, HIF-1 and HIF-2, leads to a more complete erythropoietic response.

Although HIF-PH inhibitor programs have been subsequently initiated at several other companies, we expect to remain the leader in the development of HIF-PH inhibitors for anemia, with more patients dosed and more studies conducted with roxadustat than with any other HIF-PH inhibitor.

Potential Advantages of Roxadustat for Treatment of Anemia in CKD

We believe that roxadustat has the potential to offer several safety, efficacy, reimbursement, and convenience advantages over ESAs.

Potential Safety and Efficacy Advantages

Our clinical trials to date have shown that roxadustat can treat anemia in CKD with much lower circulating EPO levels than with treatment by ESAs, mitigate the need for IV iron and treat anemia in the presence of inflammation, thereby offering potential safety and efficacy benefits over ESAs. We have incorporated several endpoints into our Phase 3 studies to further elucidate and demonstrate these and other potential clinical benefits of roxadustat.

Potential Cardiovascular Benefits

The CKD patient population is at high risk for cardiovascular events such as heart attacks and strokes. One known side effect of ESAs is elevation of blood pressure, which is particularly dangerous in this high risk patient population. In contrast, we did not observe increases in blood pressure in patients treated with roxadustat beyond the background levels observed for the comparable placebo-treated patients in a NDD-CKD Phase 2 trial. However, these data should be cautiously assessed due to the limited number of patients exposed. In Study 041, the NDD-CKD patients treated with roxadustat three times weekly for more than 12 weeks had a modest decrease in blood pressure in a subgroup analysis of our Phase 2 NDD-CKD study.

In our Phase 2 studies, we did not observe a safety signal for thromboembolic risk. In contrast to the platelet increase with ESA treatment, platelet counts reported in roxadustat-treated patients did not increase, as those with platelet levels in the top 25th percentile at baseline saw their platelet levels decrease towards normal levels while those with platelet levels in the lower 75th percentile at baseline saw their platelet levels remain stable. This finding supports our belief in a potential safety benefit over ESAs since the platelet increase with ESAs could be a contributing factor in the thromboembolic risk associated with ESAs.

In addition, in our Phase 2 clinical trials, we observed reductions in total cholesterol and an improvement in average HDL / LDL ratio. Since many CKD patients have high cholesterol levels, which contribute to cardiovascular-related morbidity and mortality, the improvement in the average HDL / LDL ratio observed with roxadustat treatment could confer a benefit to patients.

Based on our preclinical and clinical data generated to date, we believe roxadustat could offer cardiovascular benefits to a CKD patient population that typically has cardiovascular-related co-morbidities and is at a high risk for

cardiovascular events.

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Potential for Anemia Correction with Moderate EPO Levels

Randomized trials have suggested that high doses of ESAs administered in an attempt to achieve a target Hb level may cause the safety issues associated with ESA therapy. These high doses result in serum EPO levels much higher than physiological range. In contrast, the level of endogenous EPO elevation among patients treated with roxadustat is typically within or near the range observed when ascending to a higher elevation or giving blood. Treating anemia while maintaining lower circulating EPO levels may mitigate, or even avoid, the risks from ESA therapy, including cardiovascular events and death.

The following graph depicts:

1) the circulating endogenous EPO levels in natural physiologic adaptations, such as adjustment to high altitude, blood loss, or pulmonary edema [left,];

2) transient peak endogenous EPO levels estimated for CKD patients who achieved a Hb response to therapeutic doses of roxadustat in our phase 2 clinical studies [middle,];

3) the estimated peak circulating recombinant EPO levels resulting from IV ESA doses in distributions reported by the Dialysis Outcomes and Practice Patterns Study, or DOPPS, for the fourth quarter of 2011 in the United States (after bundling was initiated and when the Hb target in ESA labeling was in the range of 10-11 g/dL [right,]).

[1]Milledge & Cotes (1985) J Appl Physiol 59:360; [2]Goldberg et al. (1993), Clin Biochem 26:183, Maeda et al. (1992) Int J Hematol 55:111; [3]Kato et al. (1994) Ren Fail 16:645; [4]The transient peak endogenous EPO concentrations, or Cmax, data for roxadustat was derived from a subset of 243 patients who achieved a Hb response to roxadustat in our Phase 2 studies for whom we believe doses depicted approximated therapeutic doses. Hb target ranges for these patients were above the Hb levels specified in the current ESA package insert

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for CKD patients. Only doses in those patients whose Hb responded in Phase 2 studies are reflected in the figure. The subset of patients included 134 NDD-CKD patients treated to thrice-weekly, twice-weekly, or weekly doses of roxadustat for >16 weeks. The subset also included 109 DD-CKD patients, including incident dialysis patients whose anemia was corrected with therapeutic doses, and stable dialysis patients who received maintenance doses. Cmax of endogenous EPO levels were not measured in all patients; instead the range of EPO Cmax levels were estimated based on data derived from a more limited number of patients in whom EPO levels were measured at various roxadustat doses and among whom there was substantial variation in measured EPO levels. Accordingly, individual patients who received roxadustat may have realized EPO Cmax levels significantly above or below these estimated levels. Moreover, the estimates reflected in the graph may not be reflective or predictive of actual EPO Cmax levels or ranges that will be realized in larger populations of patients receiving roxadustat in our Phase 3 clinical trials. [5]EPO C_{max} was computed from ESA dose distributions based on Flaherty et al. (1990) Clin Pharmacol Ther 47:557.

Potential for Anemia Correction for Patient Populations that are Hyporesponsive to ESAs

Incident dialysis patients and patients who have chronic inflammation are often hyporesponsive to ESAs, which necessitates the use of higher doses of ESAs to increase Hb levels, thus increasing both safety risk and treatment cost. In contrast, the dose of roxadustat may not need to be increased in incident dialysis patients or to overcome the suppressive effects of inflammation on erythropoiesis, which we believe may confer significant safety and efficacy benefits.

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As a result of roxadustat s different mechanism of action, the ability of roxadustat to stimulate erythropoiesis does not appear to be impaired by chronic inflammation. In a preclinical model of inflammation induced by peptidoglycan-polysaccharide (PG-PS) polymers, roxadustat increased Hb levels and mean corpuscular volume (MCV), whereas Aranesp®, an ESA, and IV iron did not increase Hb or MCV. In contrast, the same doses of roxadustat and Aranesp® were both effective at raising Hb levels in the unchallenged rats (without inflammation). In addition, the ESA actually decreased MCV in the unchallenged rats, as compared to the control.

Our preclinical studies indicate that roxadustat can overcome the direct suppressive effects of inflammatory cytokines on erythropoiesis. In addition, roxadustat can reduce hepcidin levels, thus increasing absorption of iron from the GI tract and the release of iron from intracellular stores and mitigating the functional iron deficiency associated with chronic inflammation.

Furthermore, in our Phase 2 studies, patients Hb response to roxadustat was independent of the degree of underlying inflammation, as assessed by circulating levels of C-reactive protein, or CRP, a well-recognized marker of inflammation. 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. To the extent the increased levels of mortality are associated with high ESA doses, roxadustat may offer a benefit to incident dialysis patients. The median roxadustat dose in our dialysis Study 053 was 1.3 mg/kg; the Cmax of endogenous EPO levels usually associated with this dose level are comparable to the physiologic range naturally experienced by people adapting to high altitude or following blood donation. See additional information on endogenous EPO levels under the heading Potential for Anemia Correction with Moderate EPO Levels .

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Potential for Reduced Hepcidin Levels and Anemia Correction Without IV Iron

An important differentiator of roxadustat from ESAs is that roxadustat is expected to correct anemia and maintain Hb without IV iron supplementation. Patients with chronic illness, such as CKD, often suffer from absolute iron deficiency or functional iron deficiency. We believe that elevated levels of hepcidin, the major hormone that regulates iron metabolism, contributes to both absolute and functional iron deficiency.

Our Phase 2 clinical trials have shown that roxadustat can significantly reduce hepcidin levels in patients with DD-CKD and NDD-CKD. The following figure shows a reduction in serum hepcidin level of approximately two thirds, observed at week 5, in 52 incident dialysis patients treated with roxadustat.

Reduction of Serum Hepcidin Levels (Study 053) in Incident Dialysis Patients

In addition, we believe roxadustat increases the levels of proteins involved in iron uptake, release and transport. Data from our Phase 2 clinical trials indicate that oral iron supplementation alone is adequate to correct anemia during treatment with roxadustat, in contrast to ESAs which typically require IV iron supplementation. Additionally, our data indicate that unlike ESAs, roxadustat treatment does not require that patients be iron replete before initiating therapy.

Avoiding IV iron helps to avoid the significant safety risks associated with IV iron described above, and, because the cost of oral iron is significantly less than the cost of IV iron, could also confer significant costs savings.

Potential Reimbursement and Convenience Advantages

Potentially Differentiated Reimbursement Framework

ESAs are included in the MIPPA bundled payment system in the DD-CKD setting and reimbursed under Medicare Part B in the NDD-CKD setting. Based on our roxadustat data to date, we believe roxadustat has the potential to correct anemia through a differentiated mechanism of action and different therapeutic effects that create the potential to displace multiple drugs in current use (such as ESAs and IV iron), or those in development (such as agents for suppression of hepcidin). Although the bundle currently covers ESAs or oral equivalents of ESAs or other IV products encompassed by the bundle, due to the differentiated nature of roxadustat and a lack of definition in the regulations on oral equivalency, for which there may be a CMS determination later this year, it is unclear whether roxadustat will be included in or excluded from the bundle. Under MIPPA, agents that have no IV equivalent in the bundle are currently expected to be excluded from the bundle until 2024. We believe that there may be commercial benefits in either event but are unable to predict the potential benefits until further guidance from CMS becomes available.

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In the NDD-CKD setting, we expect that roxadustat, an oral treatment, should be subject to Medicare Part D, which would allow physicians to prescribe roxadustat without the financial and reimbursement risk associated with purchasing and storing injectable ESAs. We believe that this should encourage significantly greater usage outside of the dialysis setting.

Potential Reduction of Other Medications

In addition to potentially eliminating the need for IV iron, based on our Phase 2 clinical trial results to date, we believe that roxadustat has the potential to reduce the use of other medications frequently required in some CKD anemia patients, such as anti-hypertensives, anti-coagulants, and statins.

Oral Administration

Many physicians that treat CKD patients, particularly cardiologists, endocrinologists, and internists, do not typically stock or administer ESAs. An easily accessible oral agent that is dispensed by pharmacies could significantly increase the number of physicians treating anemia in patients with CKD and therefore the number of patients receiving treatment.

In addition, the oral administration of roxadustat potentially offers a significant convenience advantage for CKD patients who have yet to initiate dialysis and are therefore not regularly visiting a dialysis center. Patients can more easily self-administer medicine in any setting, rather than being subject to the inconvenience and restrictions of regular visits to physicians offices or infusion centers for treatment with ESAs.

Potential Pharmacoeconomic Advantages

Based on our Phase 2 clinical trial results to date, we believe that roxadustat s potential pharmacoeconomic advantages over ESA therapy may include safety (with a potential decrease in cardiovascular events and consequently lower associated treatment costs), lower administrative cost, reduction or elimination of IV iron and potentially other medications. If we can demonstrate any of these pharmacoeconomic advantages in our Phase 3 studies, they may help support reimbursement worldwide, including Europe and China.

The Market Opportunity for Roxadustat

We believe that there is a significant opportunity for roxadustat to address markets currently served by injectable ESAs. According to IMS Health, 2013 global ESA sales in all indications totaled $8.6 billion, driven primarily by $6.2 billion in the United States and Europe. We believe that a substantial portion of ESA sales are for CKD anemia. For example, in the U.S., EPOGEN, which is primarily used in the DD-CKD patient population, had 2014 sales of approximately $2 billion. We further believe that the number of patients requiring anemia therapy will grow steadily as the global CKD population and access to dialysis care continue to expand, particularly in China and other emerging markets including the rest of Asia, Latin America, Eastern Europe, the Middle East and the Commonwealth of Independent States.

Furthermore, we believe that there is a significant opportunity for roxadustat to address patient segments that are currently not effectively served by ESAs, such as anemia in the NDD-CKD patient population, which is substantially larger than the DD-CKD patient population. Diabetes and hypertension are the leading causes of secondary CKD. Although we estimate approximately 36% of diabetic and 20% of hypertensive CKD patients are anemic (Hb<12g/dL), we believe the majority of these patients are currently untreated for anemia since they are under the care of non-nephrology specialists, such as endocrinologists, diabetologists, cardiologists and internists, where ESA

therapies are not readily available.

We also believe that roxadustat may provide a safer option to re-establish the chemotherapy induced anemia market, which was once a market of comparable size to the DD-CKD anemia market. Other non-CKD anemias, including anemia related to inflammatory diseases, MDS and surgical procedures requiring transfusions, which are not addressed adequately with currently available therapies, could form another opportunity.

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OUR DEVELOPMENT PROGRAM FOR ROXADUSTAT

Over 1,500 subjects have been exposed to roxadustat in clinical studies, including treatment of some patients for 24 weeks in Phase 2 studies and several patients for approximately 3 years in a safety extension study.

We along with our partners, Astellas and AstraZeneca, have designed our global Phase 3 program to support regulatory approval of roxadustat in both NDD-CKD and DD-CKD patients in the United States, the European Union, Japan and China. Our US and EU Phase 3 program has an aggregate target enrollment of approximately 7,000 to 8,000 patients worldwide and is the largest Phase 3 clinical program ever conducted for an anemia product candidate. Our U.S. Phase 3 program is also designed and sized for demonstrating non-inferiority to comparators for the MACE composite safety endpoints in two separate patient pools, NDD-CKD and DD-CKD. We believe this will be required for approval in the United States for all new anemia therapies. Our Phase 3 program will study multiple patient populations, including incident dialysis patients and stable dialysis patients and will include multiple NDD-CKD studies comparing roxadustat against placebo controls. Five of the six Phase 3 studies supporting approval in the EU use the same patients that are intended to support approval in the United States. However, the EU requires shorter treatment duration and less overall patient exposure. We currently expect to complete patient enrollment in our U.S. studies by or in the first half of 2016, and that data for U.S. Phase 3 NDD-CKD studies will be reported in 2017. We currently anticipate filing for approval for roxadustat in the United States in 2018.

We have a separate roxadustat clinical development program for China and we currently plan to initiate Phase 3 studies in the second half of 2015 through our subsidiary FibroGen China. We currently anticipate filing for approval for roxadustat in China in 2016. In addition, Astellas is developing roxadustat in Japan as part of a Japan-specific development program and is currently conducting Phase 2 studies there.

Our Phase 2 Program

We have completed and analyzed six roxadustat Phase 2 studies, three in NDD-CKD patients and three in DD-CKD patients, to assess the efficacy of roxadustat to both correct anemia (correction) and maintain the Hb response (maintenance). Data from these studies have been published and presented at various medical conferences. Two of the six completed Phase 2 studies were conducted in China. The efficacy and safety data generated from our China studies were consistent with our U.S. Phase 2 studies and further contributed to the promising efficacy and safety results to date. Our collaboration partner Astellas Japan Phase 2 dialysis study in patients with CKD anemia has been completed, and data reconciliation and analysis are in process.

The data from our completed Phase 2 studies demonstrated that roxadustat achieved a clinically meaningful increase in Hb levels in anemic NDD-CKD and DD-CKD patients and maintained Hb levels in DD-CKD patients who were converted from ESA therapy. Roxadustat corrected anemia without the need for IV iron supplementation and exhibited an acceptable safety profile. Specifically, our Phase 2 studies achieved the following objectives:

- Identified optimal roxadustat dosing regimens for anemia correction and maintenance of Hb response.

- Demonstrated roxadustat s potential to treat anemia in both NDD-CKD and DD-CKD patients, including incident dialysis patients, the most unstable and high risk CKD patient population.

Generated substantial safety data, indicating that roxadustat is well tolerated, appears safe and could offer an improved cardiovascular profile relative to ESAs. Including our Phase 1, 2 and 3 studies over 1,500 subjects have been exposed to roxadustat.

Demonstrated that roxadustat may be able to treat anemia without the need for IV iron supplementation.

Demonstrated that roxadustat can reduce hepcidin levels and potentially treat anemia in a significant subset of patients with inflammation.

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The following chart summarizes the design of our completed studies in DD-CKD and NDD-CKD patients and indicates the primary objectives of each study.

Completed Phase 2 Studies

Study Number, Study Location	CKD Patient Population	Study Objective	Number of Roxadustat Patients	Number of Comparator Patients Placebo	Number of Comparator Patients ESA	Total Number of Patients in Study	Treatment Duration (Weeks)	Dose Frequencies
FGCL-4592-017 US	Non-dialysis	Correction, PK	88	28		117	4	TIW, BIW
FGCL-4592-041 US	Non-dialysis	Correction & Maintenance	145			145	16;24	TIW, BIW, QW
FGCL-4592-047 China	Non-dialysis	Correction	61	30		91	8	TIW
FGCL-4592-040 US	Stable Dialysis	Conversion & Maintenance	117	4	40	161	6;19	TIW
FGCL-4592-053 Russia, US, Hong Kong	Incident Dialysis	Correction	60			60	12	TIW
FGCL-4592-048 China	Stable Dialysis	Conversion, PK	74		22	96	6	TIW
Total			**545**			**669**		

QW = weekly; BIW = twice weekly; TIW = three times weekly

The following chart summarizes the design of our ongoing Phase 2 studies and indicates the primary objectives of each study.

Ongoing Phase 2 Studies

Study Number, Location	CKD Patient Population	Study Objective	Number of Roxadustat Patients	Number of Comparator Patients Placebo	Number of Comparator Patients ESA	Total Target Number of Patients in Study	Treatment Duration (weeks)	Dose Frequencies
1517-CL-0303* Japan	Non-dialysis	Correction	75	25		100	24	TIW, QW
1517-CL-0304* Japan	Dialysis	Maintenance	90		30	120	24	TIW
FGCL- 4592-059 US	Non-dialysis & Dialysis	Long Term Safety &	15			15	260+	TIW, BIW, QW

	Maintenance

*Studies 1517-CL-303 and -304 are being conducted by Astellas
QW = weekly; BIW = twice weekly; TIW = three times weekly

Study 017: Dose Escalating Study in NDD-CKD patients

Study 017 established proof of concept for roxadustat by showing a significant increase in Hb in a dose-dependent manner, and provided data on the relationship between roxadustat dose and Hb response. This formed the basis for the dosing rules that we applied in subsequent studies of longer duration and in a larger number of patients.

This study, a randomized, single-blind, placebo-controlled, dose-escalation study, was the first Phase 2 study to assess the safety and efficacy of a range of roxadustat doses in the correction of anemia in NDD-CKD stage 3 and 4 patients, over four weeks of treatment, and a 12-week safety follow-up period. A total of 117 patients

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(of which 96 were evaluable) were randomized sequentially into four weight-based dose cohorts: 1 mg/kg, 1.5 mg/kg, 2 mg/kg, and 0.7 mg/kg, respectively. Roxadustat was administered either twice weekly or three times weekly.

Weight Based, Three Times Weekly and Twice Weekly Dosing Leads to Hb Improvement. We tested 4 different roxadustat weight-based doses administered for four weeks with Hb measurements over a six week period. As shown in the table below, all of the patients in the highest weight-based dose cohort met the criteria for response in that they achieved Hb rise ≥ 1 g/dL in four weeks. As roxadustat achieved 100% Hb response at the 2 mg/kg dose, higher doses were not pursued in this study despite the absence of dose limiting toxicity. Roxadustat was well tolerated without any safety concerns.

Significant, Dose Dependent Increases in Hb. As shown in the table below, 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).

A p-value is a statistical measure of the probability that the difference in two values could have occurred by chance. The smaller the p-value, the greater the statistical significance and confidence in the result. Typically, results are considered statistically significant if they have a p-value less than 0.05, meaning that there is less than a one-in-20 likelihood that the observed results occurred by chance. The FDA requires that sponsors demonstrate the effectiveness and safety of their product candidates through the conduct of adequate and well-controlled studies in order to obtain marketing approval. Typically, the FDA requires a p-value of less than 0.05 to establish the statistical significance of a clinical trial, although there are no laws or regulations requiring that clinical data be statistically significant, or that require a specific p-value, in order for the FDA to grant approval.

Hb Responses to a Range of Roxadustat Doses in FGCL-4592-017

		0.7 mg/kg		1 mg/kg		1.5 mg/kg		2 mg/kg	
	Placebo	**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

BIW = twice weekly; TIW = three times weekly

Standard error of the mean, or SE, is a statistical measure of the amount that an observed mean may be expected to differ by chance from the true mean. For a population that follows a normal distribution, 68% of observed means will be within one standard error of the mean.

Dose-Dependent Reduction in Hepcidin Levels. Roxadustat reduced serum hepcidin levels in a dose-dependent fashion.

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

Study 041 demonstrated that both tier-weight and fixed starting doses can initiate anemia correction. In tier-weight based dosing for this study, we used starting doses based on the patient s body weight category: high, middle or low. This randomized, open-label Phase 2 study was designed to evaluate the efficacy and safety of roxadustat over 16 to 24 weeks in 145 NDD-CKD patients (of which 143 were efficacy evaluable), and to evaluate the effects of dosing regimens in order to determine an optimized approach to anemia correction. In this trial, we tested six different starting dose regimens: three fixed doses, and three tier-weight doses. In fixed dosing, all patients in the same cohort were given the same starting dose.

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We tested both three times weekly and twice weekly dosing frequencies for anemia correction, similar to Study 017, and further demonstrated that Hb levels can be maintained using 3 dosing frequencies (three times weekly, twice weekly and weekly) once target Hb ³ 11 g/dL was achieved. We also studied various dose adjustment rules, with dose adjustment decisions made from 5 weeks onward, and every 4 weeks thereafter, to seek the best dose titration scheme.

Hb Correction. We met the primary efficacy endpoint of cumulative number (%) of patients with a Hb response, defined as an increase in Hb ³ 1.0 g/dL from baseline and Hb ³ 11.0 g/dL at the end of treatment. Regardless of the starting dose or dose titration scheme, 92% of patients collectively from all cohorts achieved an Hb increase of at least 1 g/dL from baseline. These data suggest the doses studied are of adequate range for anemia correction. The following figure shows mean Hb levels for the six dose groups.

FGCL-4592-041 Hb Response Over Various Dosing Regimens

*** n at baseline**
TIW = three times weekly; BIW = twice weekly; QW= once weekly

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Hb Correction was Independent of Inflammation Status. In this study, in a post-hoc analysis, we observed that the magnitude of increases in Hb in response to roxadustat treatment was comparable for both patients with inflammation (elevated CRP levels) and without inflammation (normal CRP levels).

FGCL-4592-041 Mean (± SE) Maximum Change in Hb (g/dL) in 12 Weeks

This stands in contrast to treatments with ESAs, where elevated CRP is frequently associated with lower Hb response to ESAs. We observed a 30% reduction in mean hepcidin level from baseline with eight weeks of roxadustat treatment (p=0.0003), which supports our belief in roxadustat s ability to overcome inflammation and to maintain iron availability for erythropoiesis.

FGCL-4592-041 Mean (± SE) Serum Hepcidin Level (ng/mL)

Hb Correction Without IV Iron and in Patients Who Have Low Iron Levels at Study Initiation. In connection with the conduct of the study, we also evaluated several iron parameters to assess roxadustat s ability to improve Hb without the use of IV iron. At baseline, 49% of the efficacy evaluable patients did not have sufficient iron levels in the body to qualify for initiation of ESA treatment under current practice guidelines and would have been excluded from participation in all prior ESA Phase 3 trials. These patients would not be considered iron replete and are typically first treated with IV iron prior to ESA treatment initiation in an effort to ensure an

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adequate response to ESA and to minimize the risk of iron depletion. Of all patients in this study receiving roxadustat, only 38% were taking oral iron supplements. A mean Hb increase of 1.8 g/dL was achieved in the first 16 weeks of treatment without IV iron supplementation. There was no evidence for iron depletion as CHr, reticulocyte hemoglobin content or the amount of Hb in newly formed red blood cells, was maintained. Furthermore, there was evidence for improved iron utilization with increases in the MCV and increase in mean corpuscular hemoglobin concentration (MCHC) over the first 16 weeks of treatment with roxadustat from baseline ($p=0.0018$ and $p<0.0001$, respectively); both MCV and MCHC typically decrease when there is iron deficiency.

Despite the minimal use of oral iron and lack of IV iron usage, patients who were not iron replete had similar Hb responses at Week 16 as patients who were iron replete.

Reduction in Cholesterol Levels. In a post-hoc analysis of all cohorts, total cholesterol decreased during treatment with roxadustat. Mean reductions in total cholesterol were greater for patients with abnormally high cholesterol levels (> 200mg/dL). Decreases in cholesterol levels were independent of whether patients were taking statins or other lipid lowering agents. Furthermore, the HDL/LDL ratio improved with roxadustat treatment in the subgroup of patients in whom lipid profiles were conducted.

Improvement in Quality of Life. Finally, in an analysis of exploratory endpoints we observed improved quality of life in patients treated with roxadustat using a standard questionnaire called the SF-36 HRQOL. The largest positive changes from baseline occurred in the Vitality subscale (>4 points, $p<0.0001$) and Physical Component (>1.6 points, $p<0.005$) subscales of the questionnaire. We believe these data demonstrate that by correcting patients anemia, roxadustat may improve quality of life.

Study 040: ESA Conversion Study in DD-CKD Patients

Study 040 was designed to evaluate the short- and long-term dosing of roxadustat in patients on hemodialysis, or HD, treatment. These results established a conversion dose relationship between ESAs and roxadustat that will be used for Phase 3 trials. Roxadustat maintained Hb without the use of IV iron, which is generally required for the treatment of anemia by ESAs.

This randomized, single-blind study was the first roxadustat study in patients on HD treatment. Part 1 was a six week open-label Phase 2 dose ranging study in 54 patients (of which 42 were efficacy evaluable) to evaluate the impact of 4 sequential doses of roxadustat on dialysis patients Hb levels over six weeks upon switching from epoetin alfa, in comparison to those continuing prior epoetin alfa doses. Part 2 was a 19 week treatment study in 90 patients (of which 83 were efficacy evaluable) to establish optimal conversion doses and dose adjustments. Patients included had previously demonstrated a wide range of ESA-responsiveness. Study 040 met its primary endpoint in Part 1 of maintaining Hb in patients previously treated with epoetin alfa at Week 6, indicating that roxadustat can replace ESAs in DD-CKD. Study 040 also met its primary endpoint in Part 2 of maintaining Hb at Week 19, indicating that roxadustat may be effective at long-term maintenance of Hb. IV iron was prohibited in both roxadustat treated patients and ESA treated control patients during this study.

Maintenance of Hb Levels Following Conversion from ESAs. In Part 1 of this study (six week treatment), 41 patients were randomized to one of four roxadustat dose cohorts, and 13 were randomized to continue on epoetin alfa treatment. The primary endpoint was maintaining an Hb level equal to or above 0.5 g/dL below baseline Hb by the end of six weeks. As shown in the figure below, roxadustat had a dose-response effect for maintaining Hb levels. The lowest roxadustat dose cohort of 1.0 mg/kg was comparable to epoetin alfa with maintenance in 44% of roxadustat patients and 33% of the control arm, patients who continued treatment with epoetin alfa (but who were required to stop concomitant treatment with IV iron). Roxadustat doses of 1.5 mg/kg or higher were better than epoetin alfa at

maintaining Hb, with 79.2% overall maintenance and with 80% maintenance at the 1.5 mg/kg roxadustat dose, 80% maintenance at the 1.8 mg/kg roxadustat dose and 77.8% maintenance at 2 mg/kg roxadustat dose.

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In Part 2 of the study (19 week treatment), 67 patients (with baseline ESA dose requirements ranging from 7 to 164.5 U/kg three times weekly) were randomized to seven cohorts of roxadustat (with various starting doses) and 23 patients were randomized to continue on epoetin alfa. Hb correction in the roxadustat treated patients pooled across all treatment cohorts was maintained over the 19 week treatment period and was comparable to epoetin alfa. The average roxadustat dose requirement for Hb maintenance was approximately 1.70 mg/kg three times weekly.

In Part 1, which was dose ranging, we observed an increase in Hb level at doses of 1.5 to 2.0 mg/kg TIW as shown in the figures below. In Part 2, which was to establish the optimal conversion dose, we observed similar Hb maintenance between roxadustat and epoetin alfa.

FGCL-4592-040 Mean: (± SE) Hemoglobin Over Time During Anemia Treatment with Roxadustat or Epoetin Alfa in Dialysis Patients

Part 1 (6 Weeks Dosing) **Part 2 (19 Weeks Dosing)**

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In addition, in an exploratory analysis of this study we observed a dose dependent decrease in hepcidin in Part 1 of this study.

FGCL-4592-040: Change in Hepcidin Level from Baseline (ng/mL)

* n at baseline

** $p<0.05$ (comparing hepcidin change from baseline between the 2.0 mg/kg roxadustat group and the epoetin alfa group).

DD-CKD patients who switched from ESA treatment to treatment with 2.0 mg/kg roxadustat had significantly greater reduction in serum hepcidin level than those who continued ESA treatment ($p=0.038$).

FGCL-4592-040 Mean (± SE) Serum Hepcidin Level (ng/mL)

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Roxadustat Doses are Associated with Lower Circulating EPO Levels than Epoetin Alfa. The following chart shows the result of six patients who were highly responsive to epoetin alfa and participated in a substudy in which their EPO levels during treatment with roxadustat were compared to EPO levels when the patients were receiving epoetin alfa prior to randomization. Their mean peak EPO concentration after an average dose of 44 U/kg was significantly higher when patients were receiving epoetin alfa relative to when they were receiving a mean roxadustat dose of 1.3 mg/kg as illustrated below. This observation is consistent with the mechanisms of action of ESA and roxadustat, respectively, and we believe the lower EPO exposure observed with roxadustat offers potential safety benefits.

FGCL-4592-040: Mean (+SE) Plasma Erythropoietin Levels During Treatment With Roxadustat Compared With Prior Epoetin Alfa Dosing In the Same Patients (n=6)

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Maintenance of Adequate Iron Supply. The concentrations of Hb within newly formed red blood cells, or CHr, is a measure of iron availability for erythropoiesis. In an exploratory analysis of this study, without IV iron supplementation (which was prohibited in this study), CHr was maintained during roxadustat treatment but declined in patients who continued treatment with epoetin alfa. This finding indicates that unlike epoetin alfa, roxadustat allows endogenous stores of iron to provide an adequate supply to newly forming red blood cells without any IV iron supplementation.

FGCL-4592-040: Mean Reticulocyte Hb Content (CHr) Over Time in Subjects Treated with Roxadustat and Epoetin Alfa

* n at baseline

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Reduction in Total Cholesterol. Consistent with our Phase 2 studies in NDD-CKD patients, we observed in a post-hoc analysis that roxadustat reduced total cholesterol levels in stable dialysis patients, and this effect appeared durable throughout the 19 week treatment period as depicted below.

FGCL-4592-040: Mean (±SE) Total Cholesterol Over Time During Treatment of Dialysis Patients with Roxadustat or epoetin alfa-Treated

Study 053: Correction of Anemia in Incident Dialysis Patients

Incident dialysis patients are at increased risk of serious cardiovascular events and death as compared to stable dialysis patients. The mortality rate among dialysis patients is highest during the first few months of dialysis initiation, and on average, patients also require the highest doses of ESA in this period. These patients typically have high levels of systemic inflammation and require IV iron supplementation for ESA to be effective.

This randomized, open-label study was designed to evaluate the safety and efficacy of roxadustat for correction of anemia in 60 incident dialysis patients (of which 55 were efficacy evaluable) who were on dialysis for at least two weeks and not more than four months and had not been treated with ESAs, and to compare the treatment responses to roxadustat under the different iron supplementation conditions. All treatment groups in Study 053 met their primary endpoint in increasing Hb level during treatment: each cohort achieved maximum mean Hb increases from baseline, ranging between 2.8 g/dL to 3.5 g/dL, resulting from 12 weeks of roxadustat treatment. We observed that at week 12 in excess of 90% of the patients achieved a greater than 1 g/dL increase in Hb from baseline. In addition, while roxadustat corrected anemia without iron supplementation, oral iron enabled an optimal Hb response. More importantly, oral iron was as effective as IV iron for Hb correction by roxadustat. In contrast, ESA therapy requires IV iron supplementation in this patient population.

This study also showed that roxadustat can correct anemia regardless of the patient s level of inflammation as measured by CRP. At Week 12, the median weekly dose of roxadustat was 4.0 mg/kg in this trial of incident dialysis patients and is similar to the median weekly dose of 4.45 mg/kg at Week 12 in Study 040, our trial of roxadustat in stable dialysis patients. In contrast, ESA therapy typically involves higher doses at the time of dialysis initiation.

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The 48 HD patients were randomized to one of the three iron supplementation options: oral iron, IV iron or no iron. Included in the 60 patients were 12 peritoneal dialysis, or PD, patients who received oral iron. This study incorporated the same tier-weight based dosing regimen utilized in Study 041.

Hb Correction in Incident Dialysis Patients Without IV Iron Administration. All three cohorts of roxadustat treated HD patients (no iron, oral iron or IV iron supplementation) and PD patients (oral iron) achieved a significant increase in the maximum Hb change from baseline, the primary efficacy endpoint. Most importantly, the maximum increase in Hb was not significantly different between roxadustat treated HD patients supplemented with oral iron (3.5 g/dL) and those supplemented with IV iron (3.5 g/dL). In contrast, a published study of ESAs in this patient population showed that patients supplemented with oral iron achieved a Hb response comparable to no iron supplementation and significantly lower Hb response than those supplemented with IV iron. These Phase 2 data demonstrate that roxadustat, unlike ESAs, may eliminate the need for IV iron and thus avoid the side effects of IV iron in DD-CKD patients.

FGCL-4592-053: Hemoglobin Over Time During Anemia Correction with Roxadustat in Incident Dialysis Patients, with No Iron, Oral Iron, or IV Iron Supplementation

Note: Hb = hemoglobin; HD = hemodialysis; PD = peritoneal dialysis; n= number of patients

Note: *p<0.05 compared to IV iron and oral iron

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Maintenance of Iron Stores. In an exploratory analysis of this study, transferrin saturation, or TSAT, a marker of iron stores, was well maintained during this period of intensive production of red blood cells with oral iron alone, indicating that iron stores can be maintained without IV iron.

FGCL-4592-053: TSAT Over Time During Anemia Correction With Roxadustat In Incident Dialysis Patients, With No Iron, Oral Iron, or IV Iron Supplementation

Hb Correction Independent of Inflammation Status. As is typical of incident dialysis patients, about half of all patients had elevated CRP levels at baseline. In a post-hoc analysis of this study, we observed that Hb responses following roxadustat treatment were independent of baseline CRP levels. These data demonstrate that, unlike the ESAs, roxadustat has the potential to overcome the suppressive effects of inflammation on Hb responsiveness to treatment.

Significant Reduction in Hepcidin. Consistent with our other studies, in an exploratory analysis of this study we observed that patients hepcidin levels were significantly reduced, most notably in the no iron and oral iron cohorts, by $\geq$ 50% from baseline, and to a lesser extent in the IV iron cohort. At follow-up (4 weeks after stopping roxadustat), hepcidin levels returned towards baseline values. Hepcidin reduction may be one of the mechanisms for overcoming the Hb suppressive effects of inflammation by making iron more available for roxadustat-induced erythropoiesis.

China Phase 2 Studies

In China, roxadustat is known as FG-4592. We performed two Phase 2 studies in China, one trial in NDD-CKD patients, and another trial in DD-CKD patients. In these trials, Hb correction in NDD-CKD patients and Hb maintenance in DD-CKD patients replicated the results seen in the US trials.

Study 047: 8 Week Placebo-Controlled NDD-CKD

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. Iron repletion at baseline was not required and IV iron supplementation was prohibited during the trial; oral iron supplementation was allowed during the trial, similar to the corresponding US Study 041. The study used tier-weight starting dose for four weeks after which the roxadustat dose was adjusted, depending upon the initial response to treatment. Study 047 met its primary endpoint of a mean maximum increase from baseline Hb at the end of Week 8. The

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mean Hb increases at the end of eight 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 cohort compared to placebo.

FGCL-4592-047: Hb Over Time (g/dL) in Chinese NDD-CKD Patients

* n at baseline

Study 048: Stable Dialysis Conversion in China

In this multi-center, open-label, ESA-controlled study, 87 HD patients (of which 82 were efficacy evaluable) with Hb 9 to 12 g/dL previously maintained with ESAs were randomized 3:1 to roxadustat or epoetin alfa treatment groups, respectively, in three sequential dose cohorts of increasing starting doses of roxadustat. This study design was similar to Part 1 of Study 040. Study 048, an exploratory study, achieved its objective of 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 Hb responses to the roxadustat treatment of Chinese dialysis patients, with the low dose cohort were numerically similar to epoetin alfa, while the mid-dose and the high-dose cohorts each had a statistically significantly higher Hb response rate than epoetin alfa. Hb responses to the roxadustat treatment of Chinese dialysis patients (as shown in the figure below) were similar to Part 1 of Study 040 in the United States.

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FGCL-4592-048: Hb Over Time in Chinese Stable Dialysis Patients

Safety Summary

A range of roxadustat doses, up to 3.0 mg/kg in DD-CKD patients and up to 5.0 mg/kg in healthy volunteers, have been administered and all roxadustat doses have been well-tolerated. The following summarizes the safety findings of our preclinical, Phase 1 and Phase 2 studies:

No Overall Safety Signals. An independent data monitoring committee consisting of external experts in nephrology, hepatology, and biostatistics reviewed safety data from all US and Europe Phase 2 studies, and determined there were no safety signals. The overall frequency and type of treatment-emergent adverse events and serious adverse events, or SAEs, observed in these clinical studies reflect events that would be expected to occur in each of the NDD-CKD and DD-CKD patient populations. Safety analyses did not reveal any association between the rates of occurrence of cardiovascular events with roxadustat dose, rate of Hb rise or Hb level. The SAEs experienced in our studies identified by the principal investigator as possibly related to roxadustat were a stroke in a patient with a prior history of multiple strokes, one incident of vomiting, and one incident of deep venous thrombosis. The most commonly reported treatment emergent adverse events in the Phase 2 studies were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, hypertension and upper respiratory tract infection.

Of our completed Phase 2 clinical studies, four (Studies 017, 047, 040 and 048) were controlled, two with placebo and two with ESA.

For Study 017, which had a treatment period of 4 weeks, for 88 subjects on roxadustat, and 28 subjects on placebo, we observed treatment emergent SAEs, or TSAEs, in 4 patients (4.5%) on roxadustat, with 0 cardiovascular SAEs and 0 SAEs for the composite safety endpoint. There were also TSAEs in 1 patient (3.6%) in the placebo arm of the study, including 1 cardiovascular SAE and 0 SAEs for the composite safety endpoint. The composite safety endpoint (exploratory analysis) includes death, myocardial infarction, congestive heart failure, subendocardial ischaemia, cerebrovascular accident, thrombosis (fistula), arteriovenous fistula occlusion, angina pectoris, and vascular graft thrombosis. A patient may experience more than one SAE, in which case a patient is only counted once in this

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analysis. TSAEs observed in patients treated with roxadustat were arteriovenous fistula site complications, dyspnea, femoral neck fracture and non-cardiac chest pain. SAEs observed in patients treated with placebo were acute renal failure and pericarditis.

For Study 047, which had a treatment period of 8 weeks, for 61 subjects on roxadustat, and 30 subjects on placebo, we observed TSAEs in 8 patients on roxadustat (13.1%), with 0 cardiovascular SAEs, and 0 SAEs for the composite safety endpoint, and TSAEs in 4 patients on placebo (13.3%), including 1 cardiovascular SAE (3.3%), and 1 SAE (3.3%) for the composite safety endpoint. TSAEs observed in patients treated with roxadustat were chronic renal failure (4), upper respiratory tract infection (1), hyperkalaemia (2) and urinary tract infection (1). TSAEs observed in patients treated with placebo were unstable angina (1), anemia (1), retinal detachment (1), pneumonia (1) and gastritis (1).

For Study 040, for those who had a treatment period of 19 weeks, for 66 subjects on roxadustat, and 23 subjects on ESAs, we observed TSAEs in 15 patients on roxadustat (22.7%), including 1 cardiovascular SAEs (1.5%), and 8 SAEs for the composite safety endpoint (12.1%), and TSAEs in 4 patients on ESAs (17.4%), including 2 cardiovascular SAEs (8.7%), and 4 SAEs (17.4%) for the composite safety endpoint. TSAEs categorized by System Organ Class, a standard event classification, observed in patients treated with roxadustat were infections and infestations (5), metabolism and nutrition disorders (2), cardiac disorders (1), gastrointestinal disorders (1), nervous system disorders (2), respiratory, thoracic and mediastinal disorders (2), skin and subcutaneous tissue disorders (1), injury, poisoning and procedural complications (2), and psychiatric disorders (1). TSAEs categorized by System Organ Class observed in patients treated with ESA were infections and infestations (3), metabolism and nutrition disorders (3), cardiac disorders (1), respiratory, thoracic and mediastinal disorders (1), blood and lymphatic system disorders (1) and vascular disorders (1).

For Study 048 which had a treatment period of 6 weeks, for 74 subjects on roxadustat, and 22 subjects on ESAs, we observed 0 TSAEs in patients on roxadustat, including cardiovascular SAEs and for the composite safety endpoint. There were also 0 TSAEs in the patients taking ESAs.

The differences in the SAE percentages described are not considered statistically significant.

The three SAEs described above that were considered by the principal investigator to be possibly related to roxadustat did not occur in these four studies.

No Liver Enzyme Safety Signal. Liver enzymes were monitored closely in the roxadustat Phase 2 clinical development program. 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.

Extensive Evaluation of Cancer Risk. Furthermore, to assess the potential cancer risk of roxadustat, we conducted 12 tumor studies in rodents. These studies included xenograft, syngeneic, or spontaneous tumors of lung, colon, breast, pancreas, melanoma, ovarian, renal, prostate and leukemic origin, several of which are reported to be dependent on vascular endothelial growth factor, or VEGF, a protein that can be regulated by HIF for which increased levels have potentially been linked to increased tumor growth. No effect on tumor promotion was observed with roxadustat in any of the studies. In addition, roxadustat had no effect on tumor

initiation or metastasis in the studies in which these end-points were also measured. Five other HIF-PH inhibitors from our library have been evaluated in many of the same rodent tumor models as roxadustat, as well as some additional ones (35 studies of six HIF-PH inhibitors in 18 models total), with no observed effect on tumor initiation, promotion or metastasis. Finally, no significant increases in plasma VEGF levels have been observed in any of our nonclinical studies at clinically relevant erythropoietic doses of roxadustat. In March 2015, we received final reports for two-year rat and mouse carcinogenicity studies of roxadustat. Roxadustat treatment had no adverse effect on survival and did not cause carcinogenic effects in either species. Two-year rodent carcinogenicity studies that were conducted with one of the other HIF-PH inhibitors evaluated in the tumor models showed no effect on mortality or incidence of tumors.

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In clinical studies to date, we and our independent data monitoring committee have not identified any evidence to suggest tumor risk in the use of roxadustat.

No QT Prolongation. We conducted a Thorough QT study evaluating roxadustat doses up to 5 mg/kg (approximately four times the average maintenance dose studied in the NDD-CKD patient population). A lengthened QT interval is a biomarker for certain ventricular arrhythmias and a risk factor for sudden death. Our results demonstrate that roxadustat did not affect the QT interval in this study. Based on the extensive safety data collected to date, we believe that roxadustat has a favorable safety profile that supports its further development in Phase 3 clinical studies.

Our Global Phase 3 Program for Roxadustat

In support of our efforts for regulatory approval in the United States and Europe, we have initiated with our partners our global Phase 3 clinical program for roxadustat in North America, South America, Europe, Russia and Asia Pacific, with plans for expanding to other regions. FibroGen China will begin a separate Phase 3 program in China in the second half of 2015, and Astellas is responsible for Phase 3 studies upon completion of Phase 2 studies in Japan. Roxadustat is the first HIF-PH inhibitor to enter Phase 3 clinical trials. We believe that our ongoing global Phase 3 program will be the largest Phase 3 program ever conducted for an anemia agent. This broad Phase 3 program is designed to meet regulatory approval requirements of multiple regions, and is being jointly implemented with our partners, Astellas and AstraZeneca. The below chart summarizes our ongoing and planned Phase 3 clinical trials, all of which include Hb level maintenance as a study objective once correction or conversion is achieved.

Ongoing and Planned Roxadustat Phase 3 Clinical Trials

Study Number, Enrollment Start Date for Ongoing Trials	**Company Sponsor**	**Dose Frequencies for Ongoing Trials**	**Comparator**	**Estimated # of Patients to be Enrolled**	**Randomization**	**Study Objective**
United States and Europe Trials						
NON-DIALYSIS						
FGCL-4592-060, November 2012	FibroGen	TIW, BIW, QW	Placebo	Up to 600	2:1	Correction
1517- CL-0608, October 2013	Astellas	TIW, BIW, QW	Placebo	450 to 600	2:1	Correction
D5740C00001, July 2014	AstraZeneca	TIW	Placebo	2,600	1:1	Correction
1517-CL-0610, April 2014	Astellas	TIW, BIW, QW	Darbepoetin alfa	570	2:1	Correction
		NDD-CKD Sub Total		**4,000 to 4,500**		
DIALYSIS						

Stable and Incident Dialysis						
* FGCL-4592-063, February 2014	FibroGen	TIW	Epoetin alfa	Up to 750	1:1	Correction
1517- CL-0613 December 2014	Astellas	TIW	Epoetin alfa or Darbepoetin alfa	750	376:200:174	Conversion
FGCL-4592-064 January 2015	FibroGen	TIW	Epoetin alfa	750	1:1	Conversion
* D5740C00002, July 2014	AstraZeneca	TIW	Epoetin alfa	1,425	1:1	Correction & Conversion
			DD-CKD Sub Total	**3,000 to 3,700**		
NDD and DD-CKD Total for the U.S. and EU				**7,000 to 8,000**		
			China Trials			
Non- Dialysis						
FGCL-4592-808	FibroGen	TIW	Placebo	150	2:1	Correction
Stable Dialysis						
FGCL-4592-806	FibroGen	TIW	Epoetin alfa	300	2:1	Correction & Conversion
			China Total	**450****		

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TIW = three times weekly; BIW = twice weekly; QW = weekly

* Study 063 consists of only incident dialysis patients, Study 002 consists of both incident dialysis patients and conversion of stable dialysis patients. All other dialysis studies consist of only conversion of stable dialysis patients.

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

The below chart summarizes the planned and ongoing Phase 3 clinical trials by regulatory approval region, emphasizing the differences in estimated patients enrolled, minimum and average treatment durations, and resulting patient years (the product of estimated number of patients and average patient treatment duration). The studies supporting both U.S. and EU approval have extended treatment durations in the U.S. (52+ weeks) as compared with the EU (36+ weeks).

Regional Differences in Estimated Approval Requirements

Roxadustat Phase 3 Clinical Trials

			Estimated # of Patients to be Enrolled		
	Study Sponsor	**Study Number**	**United States**	**Europe**	**China**
Non-Dialysis					
	FibroGen	FGCL-4592-060	Up to 600*	Up to 600*	
	Astellas	1517-CL-0608	450-600*	450-600*	
	AstraZeneca	D5740C00001	2,600		
	Astellas	1517-CL-0610		570	
	FibroGen	FGCL-4592-808			150
NDD-CKD Sub Total by Region			Up to 3,800	Up to 1,770	150
Stable and Incident Dialysis					
	FibroGen	FGCL-4592-063**	Up to 750*	Up to 750*	
	Astellas	1517-CL-0613	750*	750*	
	FibroGen	FGCL-4592-064	750*	750*	
	AstraZeneca	D5740C00002**	1,425		
	FibroGen	FGCL-4592-806			300
DD-CKD Sub Total by Region			Up to 3,675	Up to 2,250	300
Total by Approval Region			**~7,500**	**~4,000**	**450*****
Combined U.S. and EU total			**~7,000**	**8,000**	
Minimum Treatment Duration			52 Weeks	36 Weeks	26-52 Weeks
Average Patient Treatment Duration			~1.3-1.5 years	~1 year	~32 Weeks****
Patient Years by Approval Region			**~10,000+**	**~4,000**	**~275**
Estimated Time to Complete Patient Enrollment			1H 2016		1H 2016

* Same patients used for U.S. approval and Europe approval, with extended treatment durations for U.S. approval.

**

Study 063 consists of only incident dialysis patients, Study 002 consists of both incident dialysis patients and conversion of stable dialysis patients. All other dialysis studies consist of only conversion of stable dialysis patients.

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

**** 350 patients will be treated for a minimum of 26 weeks and 100 patients will be treated for a minimum of 52 weeks.

To maximize the commercial potential for roxadustat, we have incorporated several unique elements into our Phase 3 program. We are performing the first placebo-controlled Phase 3 studies in NDD-CKD patients to potentially demonstrate the benefits of anemia therapy and safety of roxadustat compared to placebo. We are also

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performing the largest Phase 3 study in incident dialysis anemia patients, who have the highest risk for death, and are the most difficult patients to stabilize and treat for anemia in CKD. Based on data from our Phase 2 studies, we believe that roxadustat may offer a safer alternative to ESAs for this particularly vulnerable patient population. We are also evaluating the cardiovascular safety of roxadustat compared to placebo in NDD-CKD patients to first demonstrate a lack of increased risk to qualify for marketing approval by the FDA, and in these patients we will have an opportunity to measure improvements in patient outcomes with anemia therapy. Separately, we are evaluating cardiovascular safety of roxadustat compared to ESA in DD-CKD patients.

Primary and Secondary Endpoints of Our Phase 3 Program

With our partners, we have designed our Phase 3 studies to evaluate the following endpoints, most of which were evaluated in our Phase 2 studies.

Primary efficacy endpoints for anemia correction studies:

U.S.: 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.

Primary efficacy endpoints for conversion and maintenance studies:

U.S.: 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.

The primary safety endpoints for U.S. approval will be major adverse cardiac events, commonly referred to as MACE, which is a composite endpoint designed to identify major safety concerns, in particular relating to cardiovascular events such as cardiovascular death, myocardial infarction and stroke, and will be pooled across multiple studies and evaluated separately in our NDD-CKD trials and our DD-CKD trials.

We expect that our Phase 3 clinical trials supporting approval in Europe will be required to include MACE+ as a safety endpoint which, in addition to the MACE endpoints, also incorporates measurements of hospitalization rates due to heart failure or unstable angina.

We also plan to evaluate secondary endpoints, including the following:

IV iron usage in roxadustat-treated patients relative to ESA-treated patients with DD-CKD.

Red blood cell transfusion rate in roxadustat-treated relative to placebo treated patients with NDD-CKD.

Hypertension adverse events in roxadustat-treated patients relative to ESA-treated patients with DD-CKD, and blood pressure in roxadustat-treated patients relative to placebo-treated patients with NDD-CKD.

Total cholesterol, LDL-cholesterol and VLDL-cholesterol levels in roxadustat-treated patients relative to placebo-treated patients with NDD-CKD and relative to ESA-treated patients in all three anemic CKD patient populations.

Quality of life in roxadustat-treated patients relative to placebo-treated patients with NDD-CKD.

CKD progression in roxadustat-treated patients relative to placebo-treated patients with NDD-CKD.

Hospitalization rate in roxadustat-treated patients relative to placebo-treated patients with NDD-CKD and relative to ESA-treated patients in all three anemic CKD patient populations.

Rate of vascular access thrombosis in roxadustat-treated patients relative to ESA-treated patients in DD-CKD.

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Dosing Regimen

Our Phase 3 studies incorporate dosing regimens that were extensively tested in our six Phase 2 studies.

Identified Dosing Regimen. The dosing regimens for our Phase 3 studies are designed to achieve an appropriate rate and magnitude of Hb rise. In our Phase 2 studies, we explored ranges of therapeutic doses under several dosing regimens, including both tier-weight and fixed starting doses and conversion doses. Our Phase 3 program will use two tier-weight starting doses for ESA-naive patients (70 mg for patients between 45 and 70 kg and 100 mg for patients between 70 and 160 kg). Our Phase 3 dosing strategies are based on our understanding of effective approaches, derived from our Phase 2 studies, tested in modeling and simulation, and were designed to achieve Hb correction for patients with varying dose requirements in a manner that is optimal for both patients and physicians.

Dose Titration. Our Phase 3 program will use a pre-determined sequence of dose steps to titrate to a patient s particular response to roxadustat, which we found to be simple to use and sufficient to correct anemia in our Phase 2 studies. In our Phase 2 anemia correction studies, only one or two cycles of dose titration were necessary to achieve Hb correction in at least 80% of patients on average.

Dose Conversion for Dialysis Patients Previously Treated with ESAs. In our Phase 2 conversion studies, we tested a variety of starting doses and developed a mathematical relationship between baseline ESA dose and roxadustat dose required to maintain Hb levels. We use dose conversion tables derived from these Phase 2 studies to formulate starting roxadustat doses in our Phase 3 trials for patients who switch to roxadustat from ESAs.

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Dose Frequency. In preclinical and Phase 1 studies, we observed that intermittent dosing yielded optimal responses to roxadustat. Our Phase 2 studies indicated that three times weekly, twice weekly and weekly dosing regimens achieved Hb maintenance. Our Phase 3 program will dose three times weekly for all studies except two (060 and 0608) which will dose some patients twice per week and some patients once per week. We believe that intermittent dosing may help ensure a consistent and durable treatment effect for several reasons:

Greater Hb Response While Minimizing Total Drug Exposure. Early preclinical studies in rodents with a HIF-PH inhibitor (that was not FG-4592) indicated that a greater Hb response could be achieved using a lower total weekly dose with intermittent dosing compared to daily dosing. In the studies shown below, rats were dosed with HIF-PH inhibitor using either a twice weekly dosing regimen. Both a higher Hb response and a better dose response were observed in animals dosed with HIF-PH inhibitor twice weekly compared to animals that were dosed daily. Furthermore, the total weekly dose required to achieve this greater Hb response was lower.

In addition, our previous preclinical studies suggested that a wider therapeutic window was achieved with intermittent dosing compared with daily dosing. Preclinical observations such as these led us to conclude that intermittent dosing could enable a better Hb response with a lower overall drug exposure and offer a potentially wider therapeutic window.

Reduce the Risk of Changing the HIF Set Point. The HIF system has a built-in negative feedback mechanism. Genes for two of the PHD enzymes that are responsible for degrading HIF under normal oxygen conditions are actually HIF target genes. Thus, while these PHD enzymes are inhibited by hypoxia (or by a HIF-PHI), the resulting HIF activation leads to an increase in the very enzymes that are responsible for its degradation following the re-oxygenation (or potentially removal of the HIF-PHI). This negative feedback mechanism is important in enabling the HIF system to reset. However, under chronically hypoxic conditions, it has been shown that the elevation in PHD enzyme levels is maintained, leading to a change in the HIF set-point. Based on this knowledge of HIF biology, it is our belief that prolonged HIF activation by a HIF-PHI drug could similarly lead to a change in the HIF set-point, which we believe may then require an

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increased HIF-PHI dose to elicit the same HIF response. In an effort to avoid this potential risk, and to potentially prolong drug effectiveness, we have undertaken an intermittent dosing regimen.

Increase Intervals Between HIF Activation. The kinetics of HIF target gene induction (including genes encoding PHD enzymes) are variable, with some HIF target genes being induced very quickly after HIF activation and others requiring longer periods of HIF activation for significant induction. We believe that increasing the intervals between HIF activation using an intermittent dosing regimen has the potential to limit the HIF target gene response.

Potential Commercial Advantages. We expect that a dosing regimen that enables dosing concurrently with hemodialysis treatment, typically administered on a thrice weekly basis, will be more commercially attractive in the dialysis market.

Our Phase 2 studies indicated that intermittent dosing enabled anemia correction up to 24 weeks and Hb maintenance up to 19 weeks when converting a patient from ESA.

Clinical Trial Eligibility, Iron Status, and Iron Supplementation During Treatment

Unlike ESA clinical trials where patient study eligibility criteria included a requirement of adequate iron availability (measured by ferritin ³ 100 ng/mL and TSAT ³ 20%) and encouraged IV iron use, roxadustat Phase 2 studies included anemic NDD-CKD patients with ferritin ³ 30 ng/mL and TSAT³ 5% and anemic DD-CKD patients with ferritin ³ 50 ng/mL and TSAT ³10%, which permits the inclusion of patients who are iron deficient. Hemoglobin response was generally achieved in iron deficient NDD-CKD and DD-CKD patients (ferritin <100 ng/mL and TSAT< 20%) despite the fact that IV iron was not allowed during roxadustat treatment.

Our placebo-controlled Phase 3 NDD-CKD studies will use iron eligibility criteria employed in our Phase 2 studies, allow oral iron, but prohibit the use of IV iron (except as a rescue medication). In our Phase 3 DD-CKD studies, since ESA serves as the comparator and similar treatment conditions are required for roxadustat and ESA, study eligibility criteria include ferritin ³ 100 ng/mL and TSAT ³ 20%. Patients will be randomized to roxadustat or ESA, and will be encouraged to take oral iron as a first line supplemental agent. IV iron is permitted if there is inadequate Hb response to treatment and if the patient is iron deficient (ferritin <100 ng/mL and TSAT< 20%).

Status with Regulatory Agencies

In the last two years, we and our collaboration partners have had interactions with regulatory agencies in multiple territories regarding the planned development and potential path to approval of roxadustat.

Most recently, we met with the FDA in May, June and July of 2014 to discuss the overall scope of our Phase 3 development program. In order to comply with FDA s recommendation, we have designed and sized our Phase 3 program for, and will incorporate MACE composite safety endpoints that we believe will be required for approval in the United States for all new anemia therapies.

We have also discussed our Phase 3 clinical development program with three National Health Authorities in the EU and obtained scientific advice from the European Medicines Agency, which was confirmed in writing in January 2014 with respect to the adequacy of our current clinical development program to support the indication for the treatment of anemia in NDD-CKD and DD-CKD patients. We expect the MAA submission in Europe to precede our NDA filing in the United States.

Investigational New Drug and Clinical Trial Applications

Roxadustat is being studied under one Investigational New Drug Application, or IND, and several Clinical Trial Applications, or CTAs, all with a specified indication of treatment of anemia in CKD. We originally submitted the IND in the United States to the FDA in April 2006. Our collaboration partner, Astellas, submitted the CTA in

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Japan to the Pharmaceuticals and Medical Devices Agency in June 2009. We and our collaboration partners Astellas and AstraZeneca have also submitted CTAs in Europe, Latin America, Canada, Russia, and Asia, beginning in 2013.

Opportunities in Other Anemia Indications

Based on roxadustat s safety and efficacy profile to date and other potential advantages over ESAs, we believe that in addition to treating anemia in CKD, roxadustat has the potential to treat anemia associated with many other conditions, such as chemotherapy-induced anemia, anemia related to inflammatory diseases, MDS and surgical procedure requiring transfusions. We think that roxadustat, if successful, could potentially address the significant unmet need in these anemia markets.

HIF-PH Inhibitor Platform

We have been a world leader in prolyl hydroxylase inhibition since the mid-nineties. Over the past two decades, we have built a robust drug discovery platform based on our deep understanding of the inhibition of prolyl hydroxylase enzymes using small molecules. Our platform is supported not only by internal research but also by numerous academic collaborations, including a long-standing funded collaboration with a research group at the University of Oulu, Finland, headed for many years by our scientific co-founder, Dr. Kari I. Kivirikko. Dr. Kivirikko is one of the world s leading experts in collagen prolyl hydroxylases, and he remains an advisor to us.

Prior to the discovery of HIF regulation by prolyl hydroxylase activity, we had acquired compound collections from several pharmaceutical companies and assembled a diverse library of prolyl hydroxylase inhibitors to target collagen prolyl hydroxylase enzymes for fibrosis. Consequently, we were particularly well positioned to rapidly generate proof-of-concept for a number of aspects of HIF biology, and to direct medicinal chemistry efforts towards increasing potency and selectivity for the newly identified HIF-PH enzymes.

We have applied our expertise in the field of HIF-PH inhibition to develop an understanding, not only of the role of HIF in erythropoiesis, but also of other areas of HIF biology with important therapeutic implications. This consistent progression of discovery has led to findings relating to HIF-mediated effects associated with inflammatory pathways, various aspects of iron metabolism, insulin sensitivity and glucose and fat metabolism, neurological disease, and stroke. The extensive patent portfolio covering our discoveries represents an important competitive advantage.

The strength of our platform capitalizes on these internal discoveries, as well as some of the complexities of HIF biology that we and the scientific community have uncovered over the past decade. There are at least three different HIF-PH enzymes that are known to regulate the stability of HIF these enzymes are commonly referred to in the scientific literature as PHD1, PHD2 and PHD3. Studies of genetically modified mice, in which the individual HIF-PH enzymes have been deleted, have revealed that PHD2 plays a major role in the regulation of erythropoiesis by HIF. In contrast, PHD1 and PHD3 appear to play less important roles in HIF-mediated erythropoiesis, but instead have been implicated in other important biological pathways.

We believe that inhibitors selectively targeting PHD1 or PHD3 could have important therapeutic applications beyond anemia. For example, as PHD1 has been implicated in ischemic tissue injury, it has been proposed that PHD1 inhibitors may provide a novel therapeutic approach to protect organs and tissues from ischemic damage. PHD3 on the other hand has been implicated in insulin signaling, raising the possibility that PHD3 inhibitors may have therapeutic utility in the treatment of diabetes. Despite the challenges associated with selectively inhibiting just one enzyme from a closely related family, we have made important advances in the identification of selective HIF-PH inhibitors. We currently have active research programs focused on exploring the therapeutic utility of PHD1 selective inhibitors and PHD3 selective inhibitors. A lead candidate from our PHD1 inhibitor program, FG-8205, is currently in

preclinical ev