Phase 2 Studies of Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor FG-4592 for Treatment of Anemia in China

SUPPLEMENTAL INFORMATION

Supplemental Table S1. Eligibility Criteria for NDD Study

Inclusion

- Age 18 to 75 years.
- Subject had voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study had been explained and the subject had had the opportunity to ask questions.
- Chronic kidney disease with an estimated glomerular filtration rate of ≥15 and <60 mL/min/1.73 m2 using the Abbreviated 4-variable MDRD equation (KDOQI Chronic Kidney Disease Stage 3 or 4), not receiving dialysis. GFR from 10 to 15 mL/min/1.73 m^2 was acceptable with pre-approval by the medical monitor.
- The hemoglobin value in 4 screening visits and mean Hb had to be <10.0 g/dL during the screening period, with only one Hb value exception in the 4 screening visits.
- Aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ ULN during the screening period.
- Serum alkaline phosphatase (ALP) ≤2 x ULN. Subjects with serum ALP values between 1 x and 2 x ULN could be included only if bone-specific ALP (BSAP) is also elevated > ULN.
- Total bilirubin values had to be ≤ULN during the screening period.
- Serum folate and vitamin B_{12} levels above the lower limit of normal (LLN).
- Body weight: 40 to 100 kg inclusive.
- Body mass index (BMI): 16 to 38 kg/m^2 inclusive.
- Subjects taking Traditional Chinese Medicine agreed not to change dose, schedule or brand from beginning of screening through end of follow-up without prior approval by the Medical Monitor.

Exclusion

- Had received any erythropoiesis-stimulating agent (ESA) within 12 weeks prior to Day 1.
- Any clinically significant infection or evidence of an underlying infection, such as a white blood cell count > ULN during screening on two separate occasions.
- Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); or anti-hepatitis C virus antibody (anti-HCV Ab).
- History of chronic liver disease.
- Serum albumin <3 g/dL.
- New York Heart Association Class III or IV congestive heart failure.
- Myocardial infarction or acute coronary syndrome within 12 weeks prior to Day 1.
- Thromboembolic event within 12 weeks preceding Day 1.
- Uncontrolled hypertension (systolic BP >170 mm Hg or diastolic BP >110 mmHg) noted during screening on two separate occasions.
- History of malignancy, except the following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ.
- Chronic inflammatory disease other than glomerulonephritis that could impact erythropoiesis (e.g., systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it was in remission.
- Active or chronic gastrointestinal bleeding, or a known coagulation disorder.
- Hemoglobinopathy (e.g., homozygous sickle-cell disease, thalassemia of all types, etc).
- Hematological disorders, including myelodysplastic syndrome, multiple myeloma, or pure red cell aplasia.
- History of hemosiderosis, hemochromatosis or polycystic kidney disease.
- Active hemolysis or diagnosis of hemolytic syndrome.

Exclusion (cont.)

- Known bone marrow fibrosis.
- Uncontrolled or symptomatic secondary hyperparathyroidism (PTH>600ng/L).
- Seizure disorder or having received anti-epilepsy medication for seizure disorder in the 6 months prior to screening.
- Any prior or anticipated (during study period) organ transplantation.
- Anticipated elective surgery during the study period.
- Life expectancy <12 months.
- Drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that could lead to reduced absorption of study drug.
- Anticipated use of dapsone or acetaminophen (paracetamol) >2.0 g/day, or >500 mg per dose repeated every 6 hours, during the screening visit and the treatment or follow-up periods of the study.
- Androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to Day 1.
- Red blood cell transfusion within 12 weeks prior to Day 1 or anticipated need for transfusion during the dosing period.
- IV iron supplement during the screening visit and /or unwilling to withhold IV iron during the dosing period.
- Immune suppressive or steroid treatment within 12 weeks prior to Day 1.
- History of alcohol or drug abuse within the past year and inability to avoid consumption of more than three alcoholic beverages per day during the dosing period; or a positive drug screen for a substance that has not been prescribed for the subject.
- Prior treatment with FG-4592.
- Use of an investigational medication or treatment, participation in an investigational interventional study, or carryover effect of an investigational treatment expected, during the screening visit, treatment and follow-up period.
- Women who were pregnant or breastfeeding.
- Females of childbearing potential and males with sexual partners of child bearing potential, unless they were using contraception as detailed in the protocol (Section 4.5.3).
- Any medical condition that in the opinion of the investigator could pose a safety risk to a subject in this study or which could interfere with study participation.

Supplemental Table S2: Cohort Initial Dose and Dose Adjustments for NDD Study

Body Weight Tiers			Low Weight (40 to 60 kg)		Middle Weight (>60 to 80 kg)		High Weight (>80 to 100 kg)	
Low Dose C1	Start Dose		70 mg		90 mg		120 mg	
	Reduced Dose		40 mg		50 mg		70 mg	
	Adjustment	ΔHb (g/dL)	Hemoglobin Level (g/dL)					
			<11	11-13	<11	11-13	<11	11-13
		<1.0	90 mg	70mg	120 mg	90 mg	150 mg	120 mg
		≥1.0	70 mg	50 mg	90 mg	70 mg	120 mg	90 mg
High Dose C2	Start Dose		90 mg		120 mg		150 mg	
	Reduced Dose		50 mg		70 mg		90 mg	
	Adjustment	ΔHb (g/dL)	Hemoglobin Level (g/dL)					
			<11	11-13	<11	11-13	<11	11-13
		<1.0	90 mg (40-44kg)* 100 mg (>44-55 kg) 120 mg (>55-60 kg)	90mg	140 mg (>60-69kg) 150 mg (>69-80kg)	120 mg	170 mg (>80-85kg) 190 mg (>85-100kg)	150 mg
		≥1.0	90 mg	70 mg	120 mg	90 mg	150 mg	90 mg

*No escalation. Starting dose in these subjects was 2.0 – 2.25 mg/kg.

Dose reduction/dose hold for excessive erythropoiesis supersedes other dose adjustment, and can occur at any time during the Treatment Period:

- If Hb increases >2 g/dL in 2 weeks, reduce dose by approximately 40-50% (see the dose reduction table above)
- Hemoglobin >13g/dL: reduce dose by approximately 40-50% (see the dose reduction table above)
- If Hb >14, dose hold; resume at approximately 40-50% of previous dose when Hb is <12.0 g/dL (see the dose reduction table above)

Supplemental Table S3. Eligibility Criteria for DD Study

Inclusion

- Age 18 to 75 years
- Subject has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions.
- End-stage renal disease (ESRD) and receiving maintenance hemodialysis TIW for ≥4 months prior to Day 1
- Hemoglobin (Hb) values in 4 screening visits and the mean Hb must be between 9.0 and 12.0 g/dL (inclusive), and the difference between them must be ≤1.5 g/dL; only allow one hemoglobin value exception in the 4 screening visits.
- Stable doses of IV or subcutaneous injection of epoetin alfa, defined as follows:
  - Epoetin alfa dose range for 6 weeks prior to Day -7: 3000 to 20,000 IU/week
  - Stable doses of epoetin alfa (i.e., the maximum epoetin alfa dose does not exceed 130% of the lowest dose of epoetin alfa taken in this period)
- Aminotransferase levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and total bilirubin must be ≤ upper limit of normal (ULN) during the screening period
- Serum alkaline phosphatase (ALP) ≤2× ULN during screening period. Subjects with serum ALP values between 1 × and 2 × ULN may be included only if bone-specific ALP (BSAP) is also elevated > ULN
- Most recently delivered spKt/V ≥1.2 within 30 days prior to Day 7.
- Serum folate and vitamin B12 levels above the lower limit of normal (LLN)
- Body weight: 40 to 100 kg (dry weight) inclusive
- Body mass index (BMI): 16 to 38 kg/m2 inclusive
- HD subjects: dialysis vascular access via native arteriovenous fistula or synthetic graft (not via catheter)

Exclusion

- Anticipated change in hemodialysis prescription or access during the screening or dosing period of the study
- Received any erythropoiesis-stimulating agent (ESA) other than epoetin alfa within 12 weeks prior to Day 1; received epoetin alfa within 3-7 days prior to Day 1 (depending on the previous dose frequency)
- Any clinically significant infection or evidence of an underlying infection such as a white blood cell count (WBC) > ULN during screening on two separate occasions.
- Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); anti-hepatitis C virus antibody (anti-HCV Ab)
- History of chronic liver disease
- New York Heart Association Class III or IV congestive heart failure
- Myocardial infarction or acute coronary syndrome within 3 months prior to Day 1
- Thromboembolic event within 12 weeks preceding Day 1
- Inadequately controlled hypertension (systolic BP >170 mm Hg or diastolic BP >110 mmHg) noted during screening on two separate occasions.
- History of malignancy, except the following: cancers determined to be cured or in remission for ?5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ
- Chronic inflammatory disease other than glomerulonephritis that could impact erythropoiesis (e.g., systemic lupus erythematosis, rheumatoid arthritis, celiac disease), even if it is currently in remission
- Active or chronic gastrointestinal bleeding, or a known coagulation disorder
- Hemoglobinopathy (e.g., homozygous sickle-cell disease, thalassemia of all types, etc.)
- Hematological disorders, including myelodysplastic syndrome, multiple myeloma, or pure red cell aplasia
- History of hemosiderosis, hemochromatosis, polycystic kidney disease, or anephric
- Active hemolysis or diagnosis of hemolytic syndrome
- Known bone marrow fibrosis
- Uncontrolled or symptomatic secondary hyperparathyroidism (PTH>600ng/L)
- Seizure disorder or received anti-epilepsy medication for seizure disorder in the 6 months prior to screening
- Any prior organ transplantation
- Anticipated elective surgery during the study period

- Life expectancy <12 months
- Drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug
- Serum albumin <3 g/dL
- Anticipated use of dapsone or acetaminophen >2.0 g/day, or >500 mg per dose repeated every 6 hours, during the screening visit, the treatment or follow-up periods of the study
- Androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to Day 1
- Red blood cell (RBC) transfusion within 12 weeks prior to Day 1 or anticipated need for RBC transfusion during the dosing period
- IV iron supplement during the screening visitand/or unwilling to withhold IV iron during the dosing period
- History of alcohol or drug abuse; or a positive drug screen for a substance that has not been prescribed for the subject
- Prior treatment with FG-4592
- Use of an investigational medication or treatment, or carryover effect of an investigational treatment expected, during the screening visit, treatment and follow-up period.
- Women who are pregnant or breastfeeding
- Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control, unless male agrees to use of contraception
- Use of traditional Chinese medicines (TCM) druing screening to Day 1 or plans to use TCM during the study unless approved in advance by the Medical Monitor
- Any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study or which may interfere with study participation

Supplemental Table S4: Dose Adjustment (Increase) Guidelines for FG-4592 by Cohort for DD Study

		FG-4592 Dose (absolute; mg)		
Subject weight range		**Low Weight (40-60 kg)**	**Middle Weight (>60-80 kg)**	**High Weight (>80 to 100 kg)**
Cohort 1	Starting dose	70 mg	90 mg	120 mg
	Escalation dose	90 mg	120 mg	150 mg
Cohort 2	Starting dose	90 mg	120 mg	150 mg
	Escalation dose	90 mg (40-44kg)* 100 mg (>44-55kg) 120 mg (>55-60kg)	140 mg (>60-69kg) 150 mg (>69-80kg)	170 mg (>80-85kg) 190 mg (>85-100kg)
Cohort 3	Starting dose	90 mg (40-45kg) 100 mg (>45-60kg)	140 mg (>60-66kg) 150 mg (>66-80kg)	180 mg (>80-90kg) 200 mg (>90-100kg)
	Escalated dose	90 mg (40-45kg)* 100 mg (>45-55kg)* 120 mg (>55-60kg)	140 mg (60-66kg) * 150 mg (>66-71kg)* 160 mg (>71-80kg)	180 mg (>80-90kg)* 200 mg (>90-100kg)**

*No escalation. Starting dose in these subjects is 2.0 – 2.25 mg/kg

** Maximum dose allowed in protocol

Dose decreases were allowed at any time during the dosing period for excessive erythropoiesis as follows:

- **Hb >14g/dL:** FG-4592 dose was held until the subject's Hb value fell to ≤12.0 g/dL, and then resumed at approximately a 40-50% reduced dose.
- **Hb >13g/dL or Hb increased by >2 g/dL over 2 weeks**: FG-4592 dose was reduced by approximately 40-50%.