Roxadustat (FG-4592; ASP1517; AZD9941) in the Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (LR-MDS) and Low Red Blood Cell (RBC) Transfusion Burden (LTB)

Open-Label Data

David Henry[1], John Glaspy[2], Rosemary Harup[3], Moshe Mittleman[4], Amy Zhou[5], Charles Bradley[6], Gopal Saha[6], Pamela Bartels[6], Robert Leong[6], Kin-Hung P. Yu[6]

[1]Pennsylvania Hospital, University of Pennsylvania, Philadelphia, PA, USA; [2]UCLA, Los Angeles, CA, USA; [3]Royal Hobart Hospital, Tasmania, Australia; [4]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [5]Washington University School of Medicine, Saint Louis, MO, USA; [6]FibroGen Inc., San Francisco, CA, USA

Disclosures

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Anemia in Myelodysplastic Syndrome (MDS)

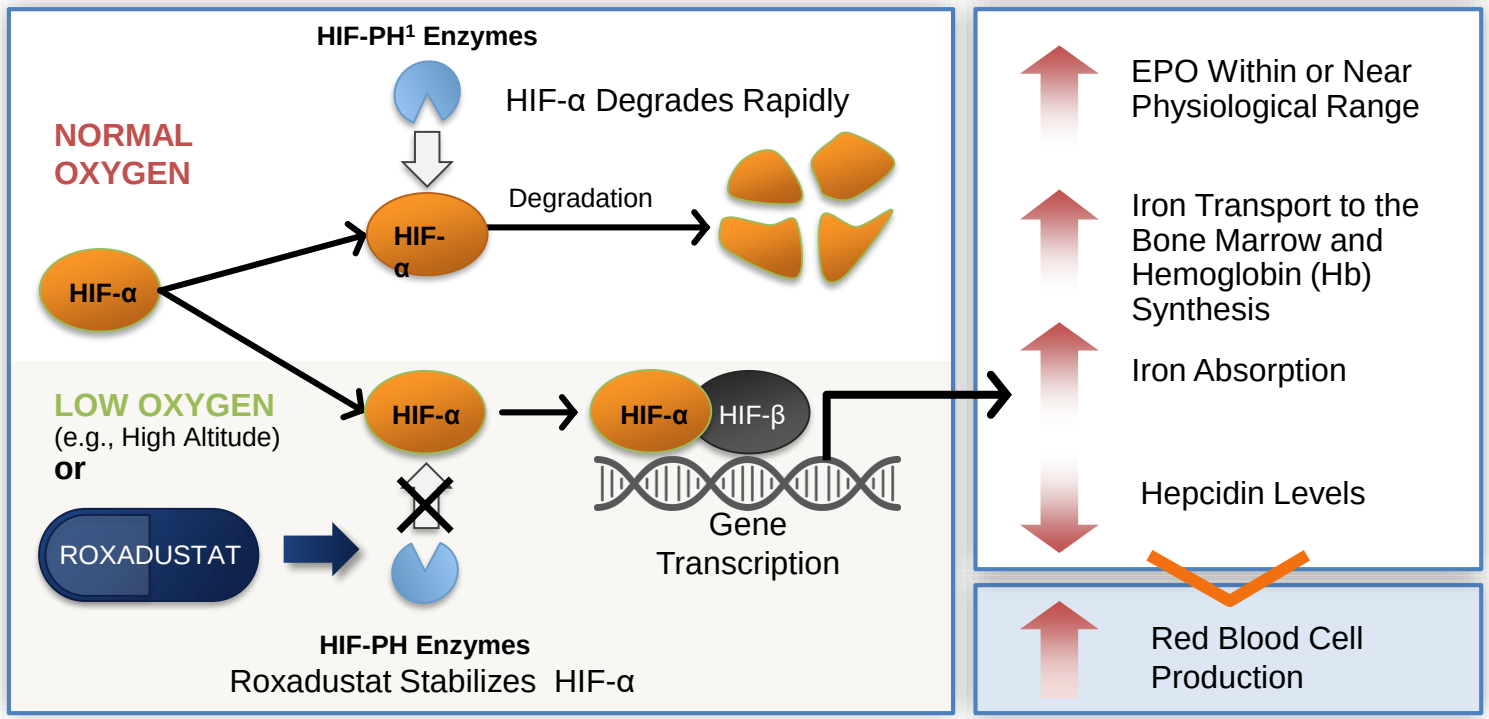
- More than 90% of MDS patients present with anemia at the time of diagnosis[1]
- Around 60% of MDS patients will experience severe anemia (hemoglobin <8 g/dL) at some point during the course of their disease[1]
- Limited anemia treatment options
  - ESA (Part of MDS anemia treatment guideline, although not approved in the U.S.)
    - Large doses may be necessary, dosing not-standardized
    - Loss of effect over time
  - RBC transfusions
    - Exposes patients to iron overload
    - Infection risk
    - Development of transfusion dependency is associated with a shorter patient survival as well as an increased risk of conversion to AML[1]

1. John M. Bennett. Consensus statement on iron overload in myelodysplastic syndromes, Am. J. Hematol. 83:858–861, 2008

Roxadustat: Novel, First-in-Class Treatment for Anemia

Roxadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor

- 2019 Nobel Prize winning science is the foundation of roxadustat
- Increases hemoglobin (Hb) by mimicking the body's natural response to low oxygen
- Studied for treatment of anemia in Stage 3 to 5 CKD patients, both dialysis and non-dialysis
- Approved in China: (dialysis 12/2018, non-dialysis 8/2019) and Japan: (dialysis 9/2019)



2019 Nobel Prize in Physiology or Medicine

"For their discoveries of how cells sense and adapt to oxygen availability."

Awarded Jointly to:

William G. Kaelin Jr.
Harvard University

Gregg L. Semenza
Johns Hopkins University

Peter J. Ratcliffe
Francis Crick Institute London

1. Hypoxia-inducible factor prolyl hydroxylase

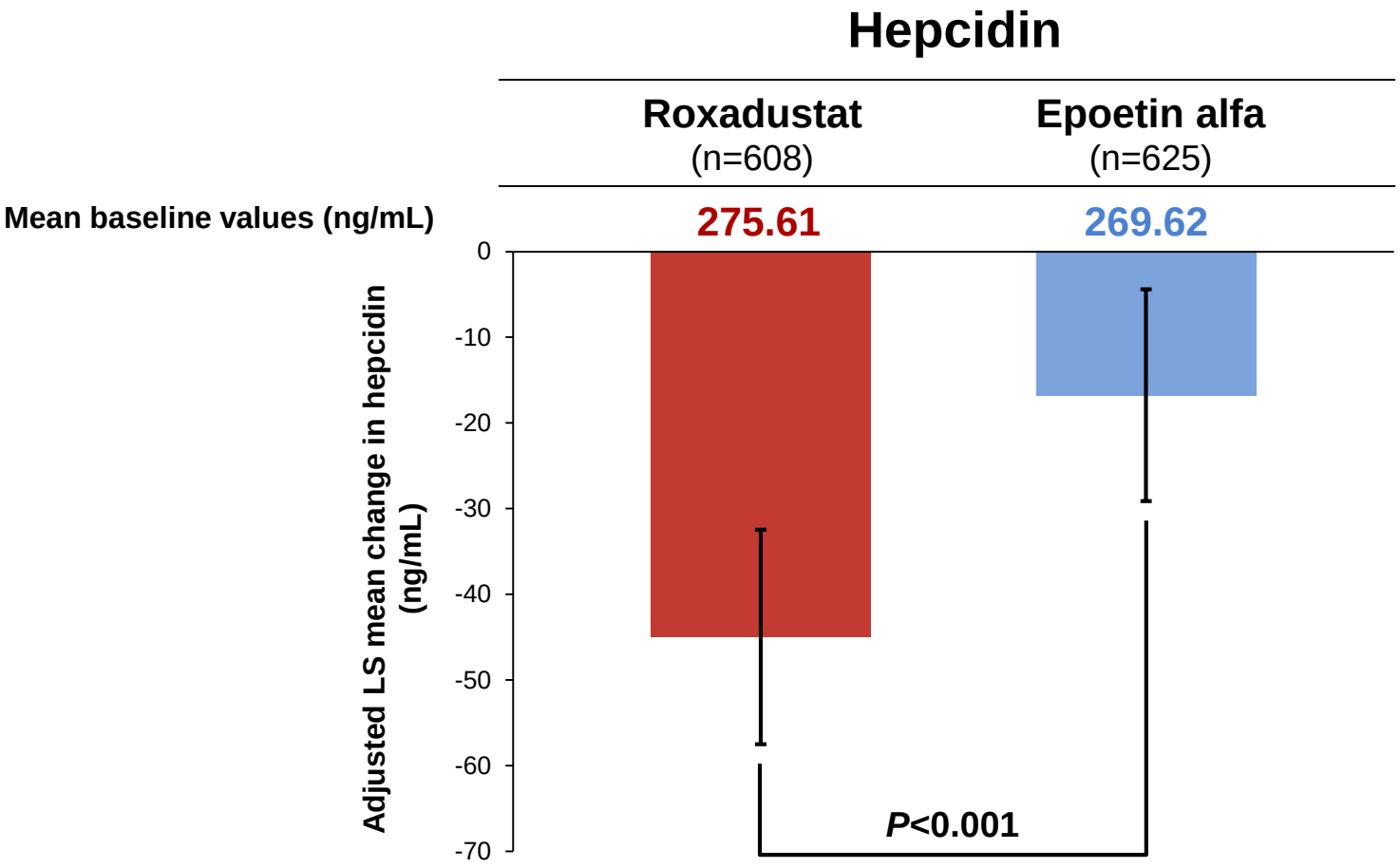
Roxadustat: Novel, First-in-Class Treatment for Anemia

Roxadustat – Oral hypoxia-inducible factor (HIF) prolyl-hydroxylase inhibitor

- Promotes erythropoiesis by increasing endogenous EPO, improving Fe regulation, and reducing hepcidin
- Roxadustat is differentiated from ESAs:
  - Regulates erythropoiesis via HIF stabilization (not an erythropoietin analogue)
  - Increase EPO receptors in the bone marrow
  - Improved iron metabolism and bioavailability
  - Effective erythropoiesis at or near physiologic EPO levels
  - Effective erythropoiesis in the presence of inflammation
  - Requires less or no IV iron
  - Orally administered, three times a week

Roxadustat Reduces Hepcidin (Phase 3 DD-CKD)

- Change from baseline to Week 24 (ROCKIES, DD-CKD Study)

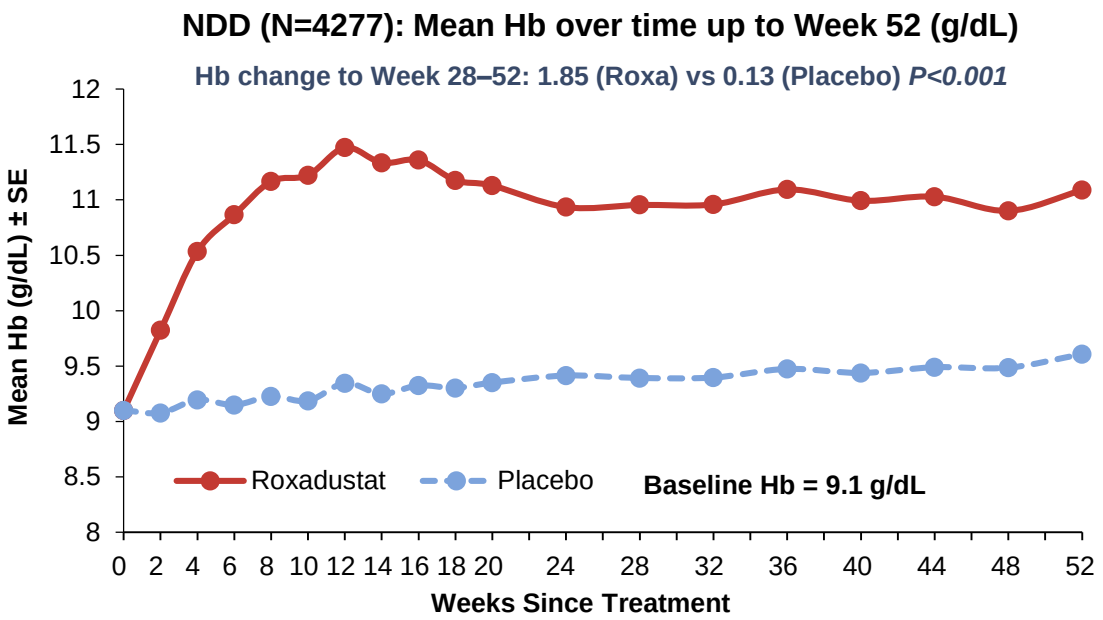


Roxadustat Global Phase 3 Development in CKD Anemia

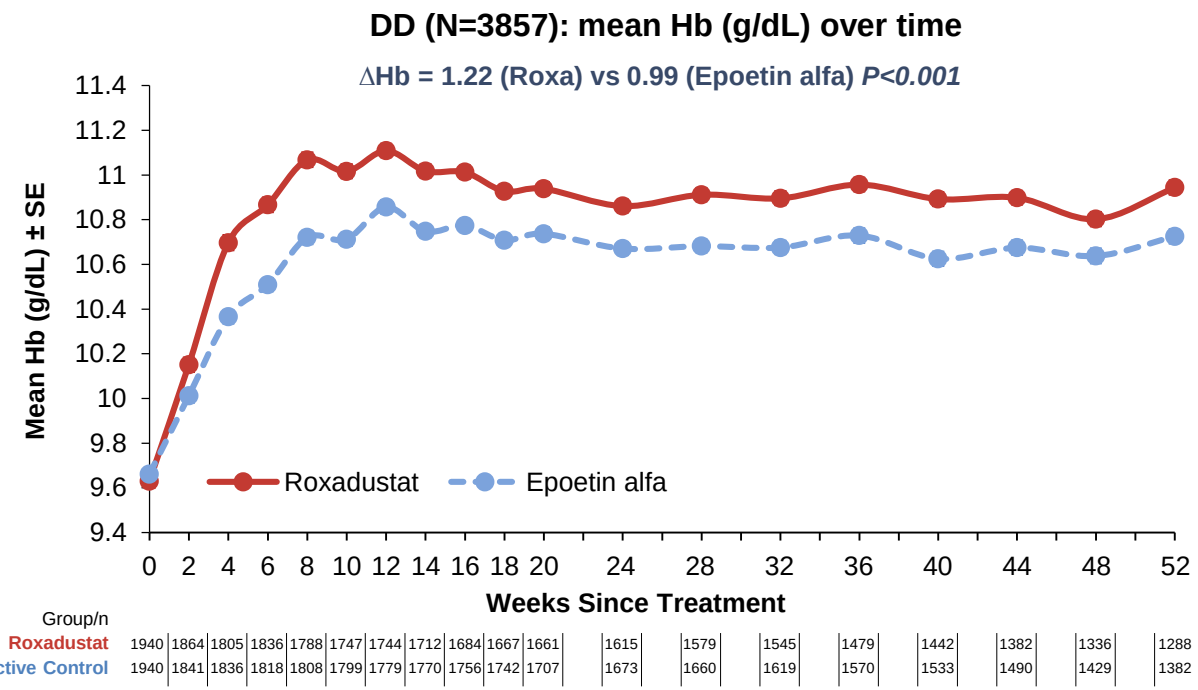
16 Phase 3 studies including 6 pivotal studies for U.S. FDA submission

- 3 placebo-controlled studies in **non-dialysis dependent** (NDD) CKD patients, pooled (N=4277, with average exposure of 1.6 years)
- 3 active-controlled vs. epoetin alfa studies in **dialysis dependent** (DD) CKD patients, pooled (N=3880, with average exposure of 1.7 years)

Roxa Corrected Anemia in ESA Naive CKD Patients



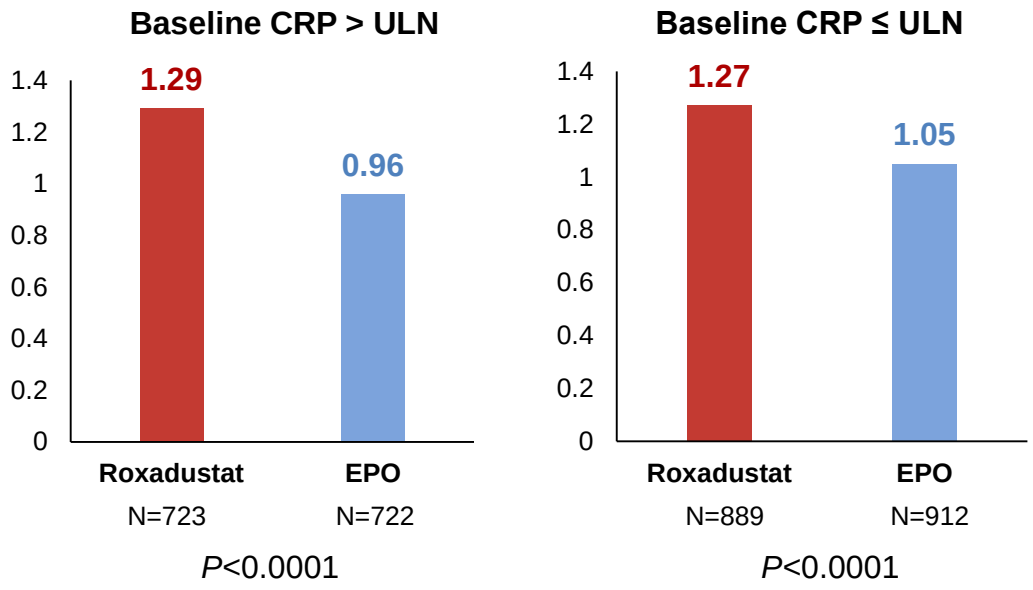
Roxa Corrected and Maintained Hb in Dialysis Patients



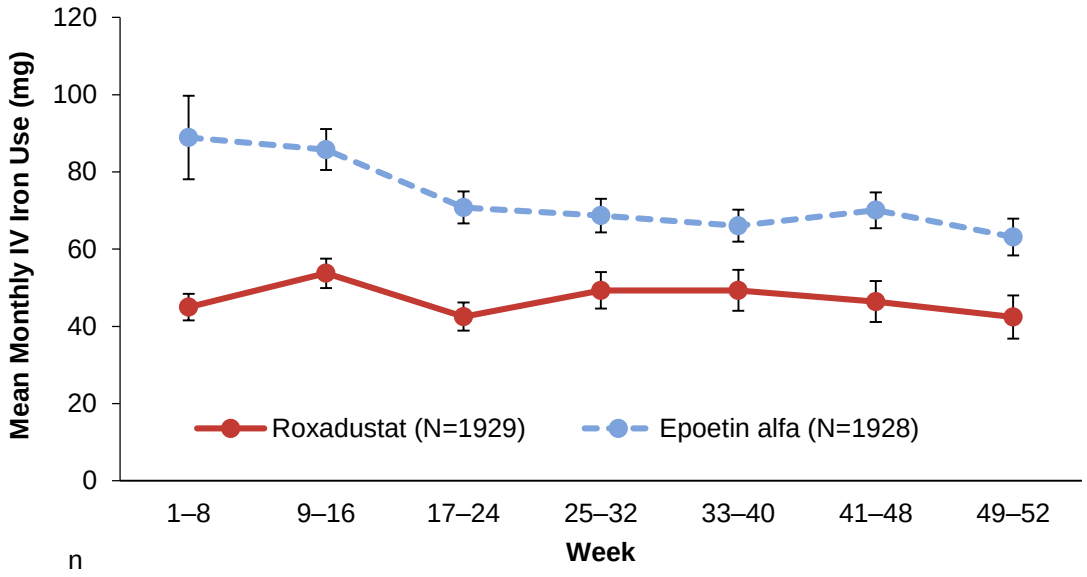
Efficacious Regardless of Inflammation and Requires Less IV Iron – Dialysis Dependent CKD Patients

- In patients with inflammation (CRP >ULN) and without inflammation (CRP ≤ULN) roxadustat achieved higher Hb increase compared to epoetin alfa
- Less IV iron was required in roxadustat patients than in patients on epoetin alfa

DD: Hb (g/dL) Change from Baseline to Weeks 28-52



DD: Less Monthly IV Iron Use in Roxadustat Patients than in Epoetin Alfa Patients



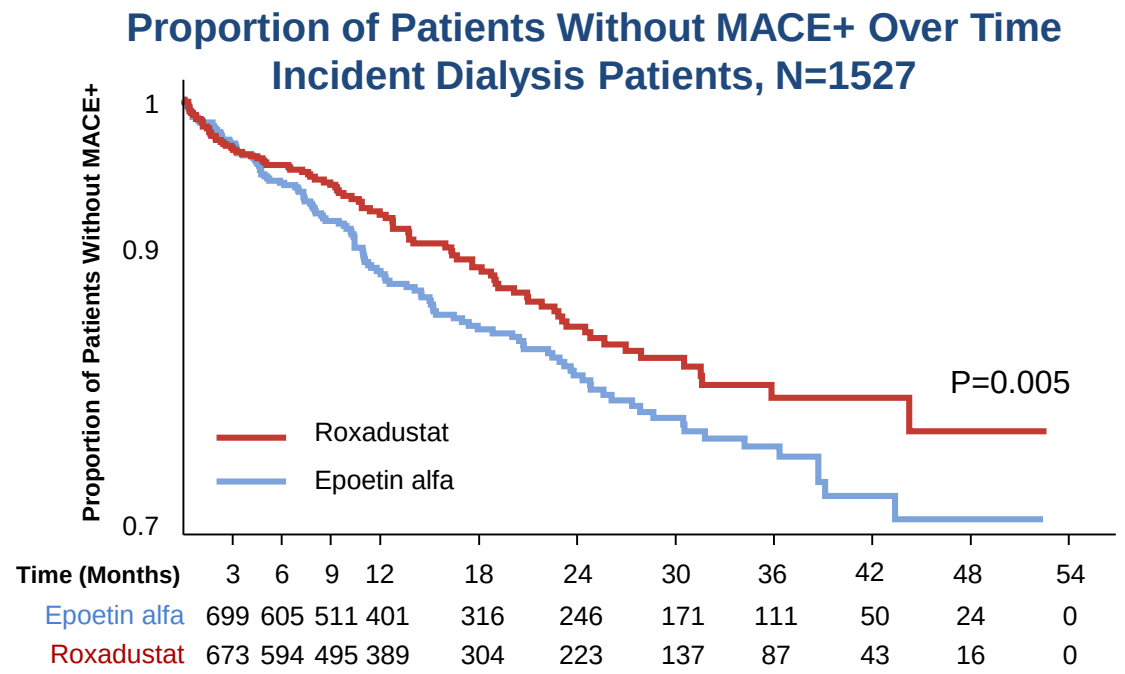
n	1–8	9–16	17–24	25–32	33–40	41–48	49–52
Roxadustat	1929	1847	1761	1681	1590	1499	1406
Epoetin alfa	1928	1885	1823	1736	1659	1582	1485

CV Safety of Roxadustat Demonstrated in CKD Patients in MACE, MACE+, All Cause Mortality Safety Endpoints in CKD Patients

- In Nondialysis patients (N=4270): Risks of *MACE, **MACE+, or all-cause mortality in roxadustat patients were comparable to placebo
- In Dialysis Dependent Patients (N=3880)
  - Risk of MACE and all-cause mortality in roxadustat patients were not increased compared to epoetin alfa in DD patients
  - Roxadustat patients had a lower risk of MACE+ than epoetin alfa patients
- In Incident Dialysis Patients (N=1527, subset of DD)
  - Roxadustat had 30% lower risk of MACE and a 34% lower risk of MACE+ than epoetin alfa
  - Roxadustat trends toward lower all-cause cause mortality risk relative to epoetin alfa in incident dialysis patients

Hazard Ratio (95% CI)*	*MACE	**MACE+	All-Cause Mortality
Non-Dialysis-Dependent (NDD), N=4270 (Placebo Comparator, ITT-a)	1.08 (0.94, 1.24)	1.04 (0.91, 1.18)	1.06 (0.91, 1.23)
Dialysis-Dependent, N=3880 (Epoetin Alfa Comparator)	0.96 (0.82, 1.13)	0.86 (0.74, 0.98) (UB<1.0, p=0.028)	0.96 (0.79, 1.17)
Incident Dialysis, N=1527 (subgroup of Dialysis Dependent (Epoetin Alfa Comparator)	0.70 (0.51, 0.96) (UB<1.0, p=0.029)	0.66 (0.50, 0.89) (UB<1.0, p=0.005)	0.76 (0.52, 1.11)

* MACE = Major adverse cardiovascular event: death, myocardial infarction, and stroke.
** MACE+ = MACE plus unstable angina hospitalization, congestive heart failure requiring hospitalization.
MACE & MACE+ events were centrally adjudicated by experts blinded to treatment assignments.



FGCL-4592-082: Phase 3 Study Design

Key Eligibility Criteria

- Adult lower risk primary MDS patients (IPSS-R ≤4.5) with <5% BM blast
- No del(5q) cytogenic abnormality
- Low transfusion burden, requiring 1-4 pRBC transfusion per 8-weeks at baseline
- No ESA within 8 weeks of Day 1
- EPO ≤400 mIU/mL
- Hb ≤10.0 g/dL

Key Endpoints

- **Primary:** Proportion of patients achieved transfusion independence (TI) for ≥8 weeks
- **Secondary:** Proportion of patients achieved a ≥50% reduction in RBC transfusion over any 8 week period
- Proportion of patients achieved TI for ≥20 consecutive weeks
- **Safety:** Review of adverse events, serious adverse events

Best Supportive Care Including RBC Transfusion (per institutional criteria) is Permitted During the Study

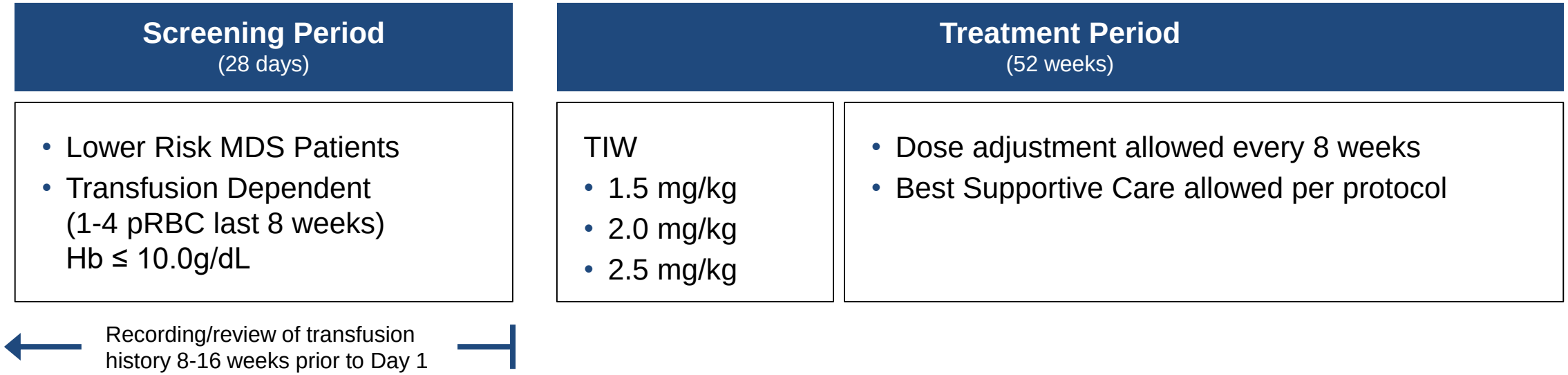
FGCL-4592-082: Study Overview

Two-Part Study:

I. Lead-in, open-label, dose finding segment; 3 sequential starting dose cohorts, 8 patients per cohort (N=24)
- Primary goal identify starting dose for DB and evaluate safety

II. Randomized, double-blind, placebo controlled segment (N= 156, 3:2 randomization)
- Primary objectives: evaluate efficacy (transfusion independence) and safety

Open-Label Lead-In



FGCL-4592-082: Baseline Characteristics (Open-Label)

	N=24
Age, Median (range), Years	73.0 (57-86)
pRBC Transfusion Burden, Median (range) Units/8-Weeks	4.0 (1-6)
MDS Duration, Median (range), Years	3.60 (0.1-15.1)
IPSS-R Risk Category, Low, n (%)	20 (83.3)
IPSS-R Risk Category, Intermediate, n (%)	4 (16.7)
IPSS-R Risk Score, Median, (Range)	2.50 (2-3.5)
Bone Marrow Blast, Median (%)	2 (0-4)
Hemoglobin, Pre-Transfusion, Median (range) g/dL	8.4 (6.7-10.2)
EPO, Median (range), mIU/mL	124.5 (26-468)
Ferritin, Median (range) (ng/mL)	1245 (349-1500)
TSAT, Median (range), (%)	54 (11-83)
Hs-CRP ≤ULN, n (%)	18 (75.0)
Hs-CRP >ULN, n (%)	6 (25.0)

FGCL-4592-082: Efficacy Assessment (Open-Label)

Efficacy Endpoints	Weeks 1-28 (Primary)	Weeks 1-52
Transfusion Independence ≥8 Weeks, n (%)	**9 (38%)**	**10 (42%)**

	Weeks 1-28	Weeks 1-52
≥50% Reduction in pRBC Over Any 8 Weeks, n (%)	**13 (54%)**	**14 (58%)**

- Median (range) number of days without transfusion: 79 (56-361) days
- No patient required IV iron
- 78% (7 of 9) patients were on 2.5 mg/kg dose at the time of transfusion independence

FGCL-4592-082: Adverse Events (Open-Label)

Summary of AEs

	N=24, n (%)
Subject with Any AE	19 (79.2)
Possibly Related (PI assessed)	6 (25.0)
AEs with CTCAE Grade 3 or Higher	5 (20.8)
Serious Adverse Events	5 (20.8)
AEs Leading to Discontinuation of Study Treatment	1 (4.2)
AEs Leading to Death	0

No Conversion to AML

Commonly Reported AEs (>1 patient)

	N=24, n (%)
Diarrhea	5 (20.8)
Dyspnea	5 (20.8)
Bronchitis	4 (16.7)
Nausea	4 (16.7)
Contusion	3 (12.5)
Hyperglycemia	3 (12.5)
Peripheral Edema	3 (12.5)
Palpitations	3 (12.5)
Abdominal Pain	2 (8.3)
Anemia	2 (8.3)
Arthralgia	2 (8.3)
AST Increased	2 (8.3)
Dizziness	2 (8.3)
Epistaxis	2 (8.3)
Headache	2 (8.3)
Insomnia	2 (8.3)
Non-Cardiac Chest Pain	2 (8.3)
Pleural Effusion	2 (8.3)
Productive Cough	2 (8.3)
Upper Respiratory Tract Infection	2 (8.3)

FGCL-4592-082: Summary/Conclusion

- ✓ Roxadustat is a novel, first-in-class HIF stabilizer for treatment for CKD anemia.
- ✓ In lower-risk, low transfusion burden MDS patients, treatment with roxadustat resulted in 8-week transfusion independence rate of 38% in the first 28 weeks; 54% of patients had ≥50% reduction in pRBC transfusions over any 8 weeks, from baseline.
- ✓ Roxadustat was generally well tolerated in each dose cohort.
- ✓ 2.5 mg/kg dose level was selected as starting dose for DB phase because 78% (7 of 9) patients were on this dose at the time of TI in open label phase, with no dose-limiting toxicity encountered.
- ✓ Roxadustat is a potential new therapy for treatment of anemia in lower-risk, transfusion dependent MDS patients (roxadustat is not approved to treat MDS in any country).

Acknowledgements

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And, many other contributors who made Roxadustat clinical studies possible.

Thank You