# Roxadustat for the treatment of anemia in dialysis patients

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# Presenter and Commercial Support Disclosure

- Presenter's Name: Mark Ho
- I have no current or past relationships with commercial entities
- Speaking fees for the current program:
  - I have received a speaker's fee from CSHP for this learning activity
- This program has received no financial or in-kind support from any commercial or other organization

# Learning Objectives

By the end of this session, the learner will be able to:

- Describe the mechanism of action of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PH Inhibitors)
- Describe the trial methodology and outcomes for roxadustat in the article, Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

# Anemia in CKD

| | | |
|---|---|---|
| Functional iron deficiency | Iron replacement<br>- PO Iron<br>- IV Iron | **HIF-PH Inhibitors** |
| Erythropoietin (EPO) deficiency | Erythropoiesis-Stimulating Agents<br>- Darbepoetin alfa<br>- Epoetin alfa | |

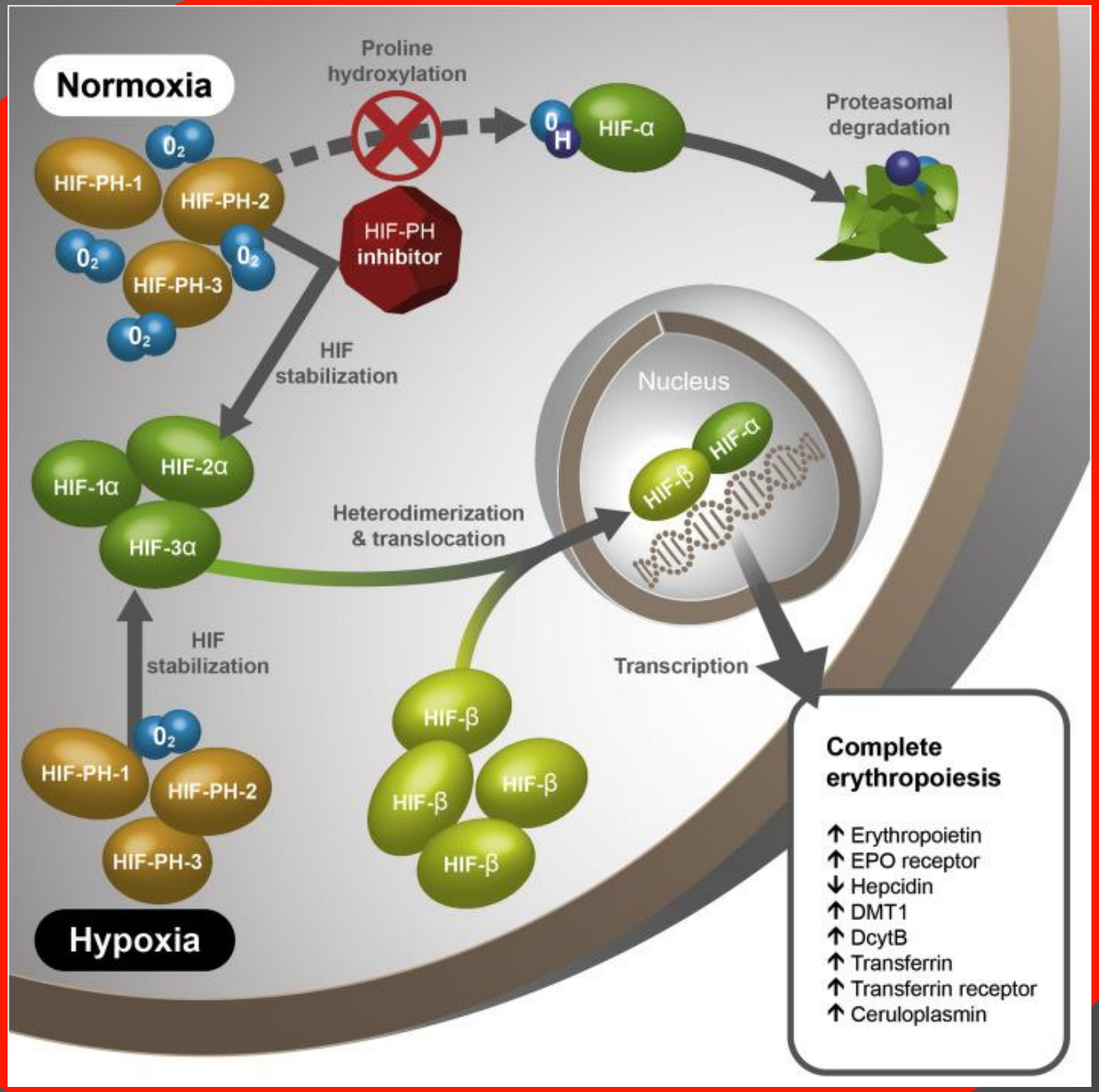
**HIF** = Hypoxia-inducible factor

**PH** = Prolyl hydroxylase

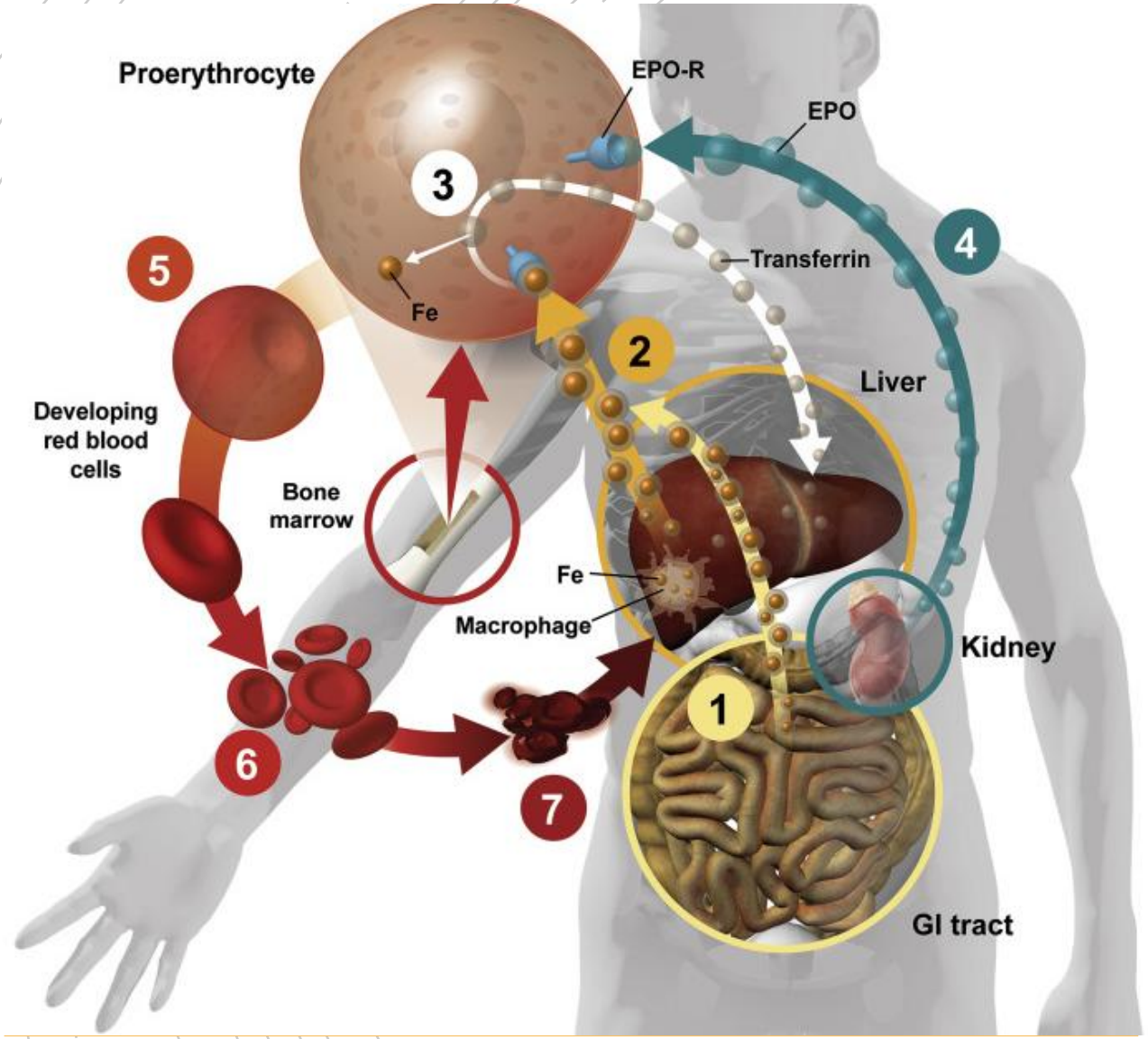
**O** = oxygen

**DMT1** = divalent metal transporter 1

**DcytB** = duodenal cytochrome b




Am J Kidney Dis. 2017;69(6): 815-826




1. Improved intestinal iron absorption
2. Improved iron transport to bone marrow
3. Increased iron deposition into erythrocytes
4. Increased endogenous EPO production

**Resulting in increased fully functional mature erythrocytes** (5-7)

Am J Kidney Dis. 2017;69(6): 815-826

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

N Engl J Med 2019;381: 1011-1022

- Randomized, open-label, non-inferiority trial
- Conducted in China
- Sponsored by drug manufacturer
- 304 patients
- 18-75 years old with ESRD on dialysis (HD/PD) and a stable dose of epoetin alfa
- Randomized 2:1 to receive
  - Roxadustat
  - Epoetin alfa

| Characteristic | Roxadustat (N = 204) | Epoetin Alfa (N = 100) |
|---|---|---|
| Age — yr | 47.6±11.7 | 51.0±11.8 |
| Male sex — no. (%) | 126 (61.8) | 58 (58.0) |
| Type 2 diabetes — no. (%) | 30 (14.7) | 17 (17.0) |
| Weight — kg | 62.8±11.8 | 61.5±9.9 |
| Hemoglobin | | |
| Mean value — g/dl | 10.4±0.7 | 10.5±0.7 |
| Distribution — no. (%) | | |
| <10.0 g/dl | 56 (27.5) | 29 (29.0) |
| ≥10.0 g/dl | 148 (72.5) | 71 (71.0) |
| Baseline epoetin alfa dose | | |
| Mean value — IU/wk | 7582±2931 | 7597±2931 |
| Distribution — no. (%) | | |
| <8000 IU/wk | 99 (48.5) | 50 (50.0) |
| ≥8000 IU/wk | 105 (51.5) | 50 (50.0) |
| Dialysis method — no. (%) | | |
| Hemodialysis | 182 (89.2) | 89 (89.0) |
| Peritoneal dialysis | 22 (10.8) | 11 (11.0) |
| Duration of dialysis — yr | 4.5±3.5 | 4.4±2.9 |

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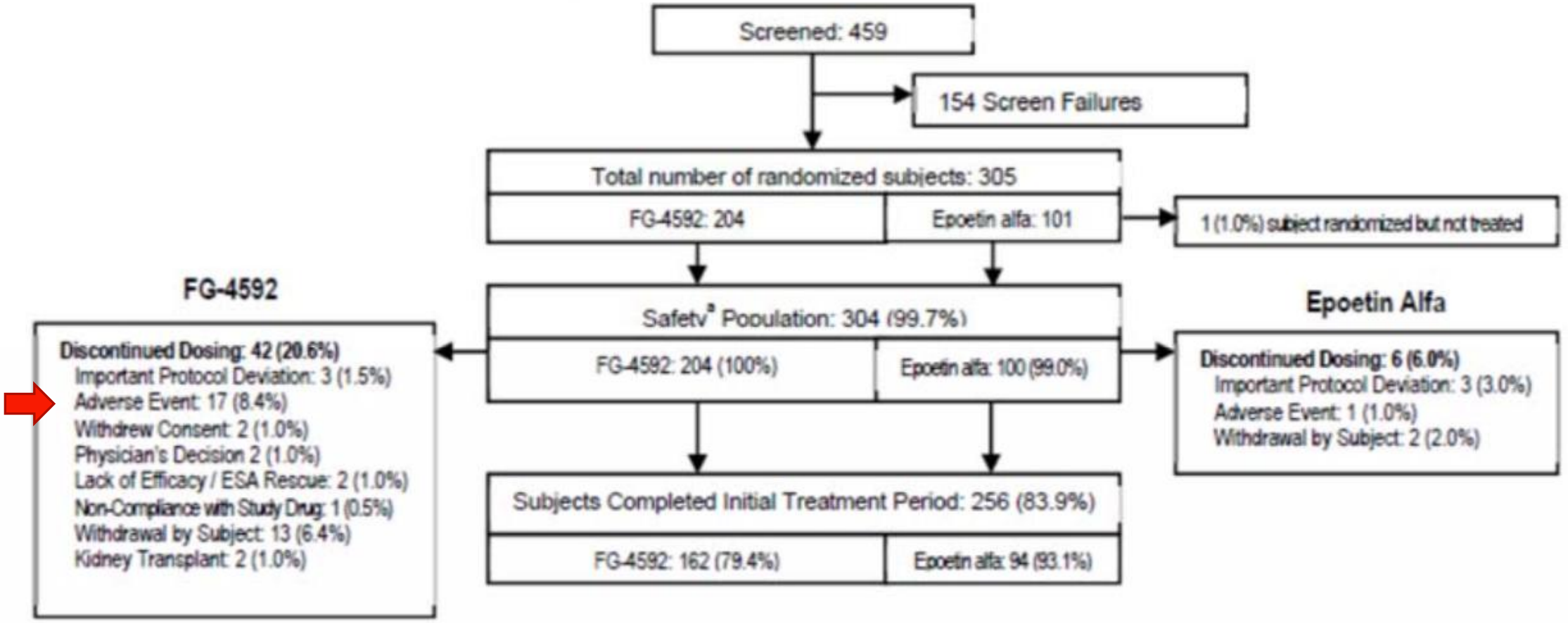
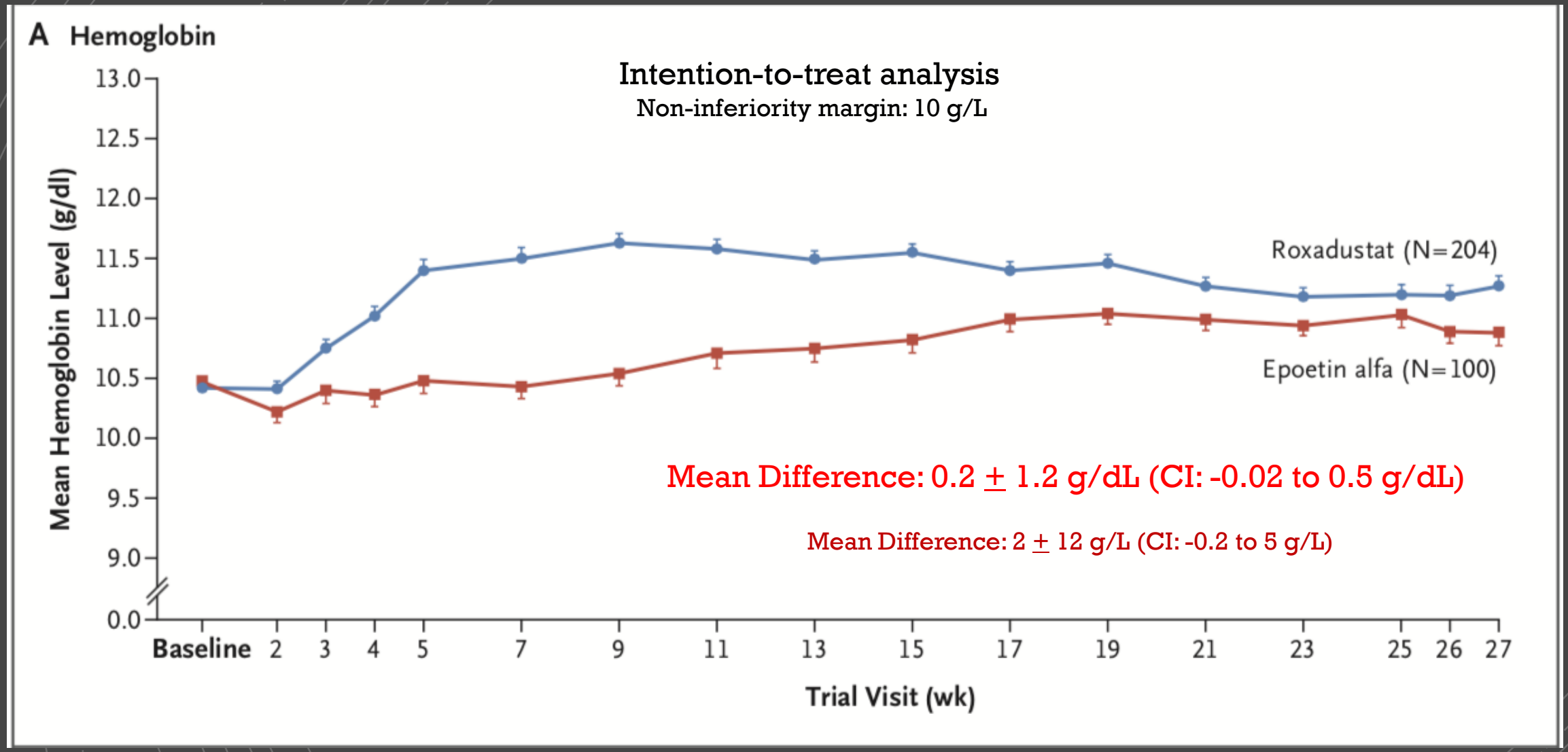
**Figure 1. FGCL-4592-806 Disposition Flow Chart**




Note: The percentage is calculated based on the number of randomized subjects.

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# Iron parameters

| | Roxadustat | | Epoetin Alfa | | Treatment difference (95% CI) |
|---|---|---|---|---|---|
| | End of treatment assessment | Change from baseline (least-squares mean) | End of treatment assessment | Change from baseline (least-squares mean) | |
| **Iron (umol/L)** | 15.2 ± 8.1 | 0.1±8.3 (0.6±0.7) | 10.6±4.0 | -3.7±7.2 (-3.9±0.5) | **4.4±0.7 (3.0-5.9)** |
| **Transferrin (g/L)** | 2.29±0.66 | 0.4±0.48 (0.38±0.05) | 1.86±0.45 | -0.04±0.36 (-0.05±0.04) | **0.43±0.05 (0.32-0.53)** |
| **TIBC (umol/L)** | 57.4±16.5 | 10.0±11.9 (9.5±1.2) | 46.6±11.3 | -1.1±9.0 (-1.2.1) | **10.7±1.3 (8.1-13.3)** |
| **Transferrin saturation (%)** | 28.0±15.8 | -5.7±15.4 (-4.5±1.2) | 23.0±8.5 | -7.6±13.8 (-8.7±1.0) | **4.2±1.4 (1.5-6.9)** |
| **Ferritin (ug/L)** | 373±470 | -119±208 (-99±19) | 294±294 | -136±220 (-133±21) | 35±24 (-12-82) |

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# Adverse effects

| Event | Roxadustat (N = 204) | Epoetin Alfa (N = 100) | Total (N = 304) |
|---|---|---|---|
| | *number of patients (percent)* | | |
| Adverse events | | | |
| Any adverse event during treatment | 96 (47.1) | 38 (38.0) | 134 (44.1) |
| Upper respiratory tract infection | 37 (18.1) | 11 (11.0) | 48 (15.8) |
| Hypertension | 25 (12.3) | 16 (16.0) | 41 (13.5) |
| Hyperkalemia† | 15 (7.4) | 1 (1.0) | 16 (5.3) |
| Chest discomfort‡ | 13 (6.4) | 0 | 13 (4.3) |
| Vomiting | 12 (5.9) | 2 (2.0) | 14 (4.6) |
| Asthenia | 12 (5.9) | 2 (2.0) | 14 (4.6) |
| Alanine aminotransferase increased | 11 (5.4) | 4 (4.0) | 15 (4.9) |
| Dizziness | 10 (4.9) | 6 (6.0) | 16 (5.3) |
| Hypotension | 10 (4.9) | 6 (6.0) | 16 (5.3) |
| Muscle spasms | 5 (2.5) | 5 (5.0) | 10 (3.3) |

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## Supplemental Table S4: Potassium Levels by Treatment Arm during Treatment Period

| Potassium Categories (mmol/L) | Baseline | | Week 13 | | Week 27 | | Historical comparator cohort ** |
|---|---|---|---|---|---|---|---|
| | Roxadustat n (%) | Epoetin-alfa n (%) | Roxadustat n (%) | Epoetin-alfa n (%) | Roxadustat n (%) | Epoetin-alfa n (%) | |
| **≤ 5.5** | 150 (73.5) | 69 (69.0) | 124 (69.3) | 73 (75.3) | 120 (75.9) | 64 (70.3) | (80.4) |
| **> 5.5 to 6.0** | 30 (14.7) | 22 (22.0) | 34 (19.0) | 15 (15.5) | 22 (13.9) | 14 (15.4) | (12.5) |
| **> 6.0 to 6.5** | 12 (5.9) | 7 (7.0) | 11 (6.1) | 5 (5.2) | 9 (5.7) | 8 (8.8) | (4.9) |
| **> 6.5** | 12 (5.9) | 2 (2.0) | 10 (5.6) | 4 (4.1) | 7 (4.4) | 5 (5.5) | (2.2) |

N Engl J Med 2019;381: S15

## Supplemental Table S4: Potassium Levels by Treatment Arm during Treatment Period

| Potassium Categories (mmol/L) | Baseline | | Week 13 | | Week 27 | | Historical comparator cohort ** |
|---|---|---|---|---|---|---|---|
| | Roxadustat n (%) | Epoetin-alfa n (%) | Roxadustat n (%) | Epoetin-alfa n (%) | Roxadustat n (%) | Epoetin-alfa n (%) | |
| **≤ 5.5** | 150 (73.5) | 69 (69.0) | 124 (69.3) | 73 (75.3) | 120 (75.9) | 64 (70.3) | (80.4) |
| **> 5.5 to 6.0** | 30 (14.7) | 22 (22.0) | 34 (19.0) | 15 (15.5) | 22 (13.9) | 14 (15.4) | (12.5) |
| **> 6.0 to 6.5** | 12 (5.9) | 7 (7.0) | 11 (6.1) | 5 (5.2) | 9 (5.7) | 8 (8.8) | (4.9) |
| **> 6.5** | 12 (5.9) | 2 (2.0) | 10 (5.6) | 4 (4.1) | 7 (4.4) | 5 (5.5) | (2.2) |

N Engl J Med 2019;381: S15

# Points to consider

- Mostly Chinese patients
- Drop-out in roxadustat group > epoetin alfa group
- Average hemoglobin already in target range 90-120 g/L (BC Renal target 95-115 g/L)
- No IV iron given
- Hyperkalemia
- Long-term effects for efficacy and safety

# Conclusion

- Roxadustat was shown to be non-inferior to epoetin alfa for the management in anemia in hemodialysis patients
- It is unclear whether roxadustat can reduce the need for iron supplementation
- Hyperkalemia is a potential side effect
- Further studies and post-marketing surveillance will be needed to support its efficacy and safety