# MODERATE HEPATIC IMPAIRMENT HAS ONLY A MINOR IMPACT ON THE PHARMACOKINETICS OF ROXADUSTAT, AN ORAL HYPOXIA INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITOR

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## Introduction and Objectives

Roxadustat (FG–4592/ASP1517) is a hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), which is currently in phase 3 development for the treatment of anemia associated with dialysis and nondialysis dependent chronic kidney disease (CKD).[1]

This study was designed to evaluate the effects of moderate hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of roxadustat compared to subjects with normal hepatic function.

## Methods

### Subjects

- Adult male or female subjects aged 18-80 y; body mass index (BMI) 18.5-34 kg/m$^2$.
- Eight subjects with moderate hepatic impairment (Child-Pugh Score [CP] between 7 and 9 [Class B]) and 8 healthy subjects with normal hepatic function (matched for BMI [± 15%], age [± 5 y] and sex).

### Study Design

- Open–label, single-dose study. All subjects received a single 100 mg oral roxadustat dose under fasting conditions.
- Blood sampling: Roxadustat PK: predose and up to 96 h (normal hepatic function) or 144 h postdose (moderate hepatic impairment); Unbound concentrations: 3, 12 and 24 h postdose in both groups; endogenous erythropoietin concentration (EPO): predose and up to 96 h (normal hepatic function) or 144 h postdose (moderate hepatic impairment).
- Urine sampling: Roxadustat PK: predose and up to 96 h (normal hepatic function) or 144 h postdose (moderate hepatic impairment).
- Plasma and urine concentrations of roxadustat determined by validated LC-MS/MS. Unbound fraction of roxadustat determined by equilibrium dialysis. EPO concentrations determined by validated Immunolite assay.
- Safety and tolerability were assessed throughout the study.

### Assessments

- Noncompartmental PK (total and unbound) and PD parameters: maximum plasma concentration ($C_{max}$); area under the curve extrapolated to infinity ($AUC_{inf}$); time of $C_{max}$ ($t_{max}$); terminal elimination half-life ($t_{1/2}$); fraction unbound ($f_u$); apparent total body clearance (CL/F); apparent volume of distribution ($V_z$/F); renal clearance ($CL_R$); percentage of dose excreted into urine extrapolated to infinity ($Ae_{inf}$%); maximum observed EPO concentration ($E_{max}$); EPO AUC from time zero to the last measurable sample ($AUC_{E,last}$); time of $E_{max}$ ($t_{max,E}$). Baseline corrected EPO values obtained by subtracting baseline from measured value.
- Geometric least-squares mean ratios (GMR) (hepatic impaired/normal function) and associated 90% confidence intervals (CI) for log-transformed $AUC_{inf}$ and $C_{max}$ of total and unbound roxadustat, $AUC_{E,last}$ and $E_{max}$ were calculated using a linear mixed effects model controlling for hepatic function status (normal or moderate impaired), sex, age and BMI as fixed effects and subject as random effect.

## Results

### Subject Disposition

- 8 subjects with moderate hepatic impairment (Child-Pugh Scores of 7, 8 and 9 for 2, 2 and 4 subjects, respectively) matched per protocol to 8 subjects with normal hepatic function received study treatment and completed the study.

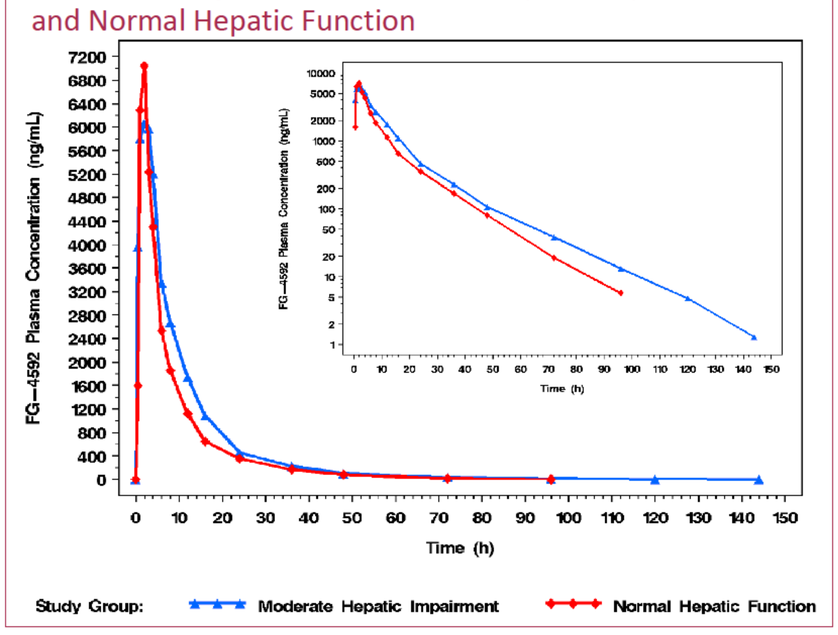
## Results (continued)

- Moderate hepatic impairment: median age 62.5 y (range 36-67); median BMI 28.3 kg/m$^2$ (range 21.1-32.3); median weight 77.5 kg (range 52-108); all White; 62.5% (5/8) male.
- Normal hepatic function: median age 57.5 y (range 35-64); median BMI 28.4 kg/m$^2$ (range 24.0-31.2) median weight 85.5 kg (range 68-98); all White; 62.5% (5/8) male.

### Roxadustat Pharmacokinetics

- In subjects with moderate hepatic impairment, roxadustat $AUC_{inf}$ and $C_{max}$ were 23% higher and 16% lower respectively compared to subjects with normal hepatic function (Fig. 1, Table 1). The differences do not appear to be of clinical significance.

**Figure 1:** Mean Plasma Roxadustat Concentration-Time Profiles in Subjects with Moderate Hepatic Impairment and Normal Hepatic Function




- Mean $t_{1/2}$ was longer in subjects with moderate hepatic impairment. Further, the intersubject variability (CV%) on CL/F, $V_z$/F and $t_{1/2}$ was approximately 2-fold higher.
- Unbound $AUC_{inf}$ and $C_{max}$ were 70% and 16% higher in subjects with moderate hepatic impairment, though variability was also higher in subjects with moderate hepatic impairment.
- The percentage of unchanged roxadustat excreted in urine and renal clearance were slightly higher in subjects with moderate hepatic impairment, whereas the renal clearance of unbound roxadustat appeared not to be affected.

**Table 1:** Statistical Assessment of Roxadustat PK Parameters in Subjects with Moderate Hepatic Impairment and Normal Hepatic Function

| Parameter | Moderate Hepatic Impairment‡ (n=8) | Normal Hepatic Function‡ (n=8) | GMR (%) (90% CI) hepatic impaired/ normal |
|---|---|---|---|
| Total | | | |
| $C_{max}$ (ng/mL) | 6975 (22%) | 8498 (26%) | 83.6 (67.5, 104) |
| $AUC_{inf}$ (ng·h/mL) | 63693 (49%) | 49807 (30%) | 123 (86.1, 175) |
| $t_{max}$ (h) | 2.00 (0.50 – 3.0) | 1.50 (1.0 – 2.0) | - |
| $t_{1/2}$ (h) | 17.7(40%) | 12.8(18%) | - |
| CL/F (L/h) | 1.92 (47%) | 2.13 (23%) | - |
| $V_z$/F (L) | 49.9 (63%) | 40.3 (36%) | - |
| $CL_R$ (L/h) | 0.0475 (77%) | 0.0320 (39%) | - |
| $Ae_{inf}$ (%) | 2.41 (73%) | 1.58 (40%) | - |
| Unbound | | | |
| $C_{max,u}$ (ng/mL) | 78.4 (22%) | 67.7 (20%) | 116 (93.1, 145) |
| $AUC_{inf,u}$ (ng·h/mL) | 708 (44%) | 397 (24%) | 170 (119, 243) |
| $CL_{R,u}$ (L/h) | 4.12 (73%) | 3.99 (39%) | - |
| $f_u$ (%) | 1.13 (14%) | 0.809 (8.1%) | - |

‡ Mean (CV%); Median (range) for $t_{max}$;
Subscript u denotes PK parameters for unbound drug.

## Results (continued)

### Roxadustat Pharmacodynamics

- In subjects with moderate hepatic impairment, baseline-corrected EPO $AUC_{E,last}$ and $E_{max}$ were respectively 31% and 48% lower than in subjects with normal hepatic function (Fig. 2, Table 2). Intersubject variation in EPO exposure was approximately 2- to 3- fold higher.
- EPO levels returned to baseline levels within 48 h.

**Figure 2:** Mean (SD) EPO Concentrations in Subjects with Moderate Hepatic Impairment and Normal Hepatic Function

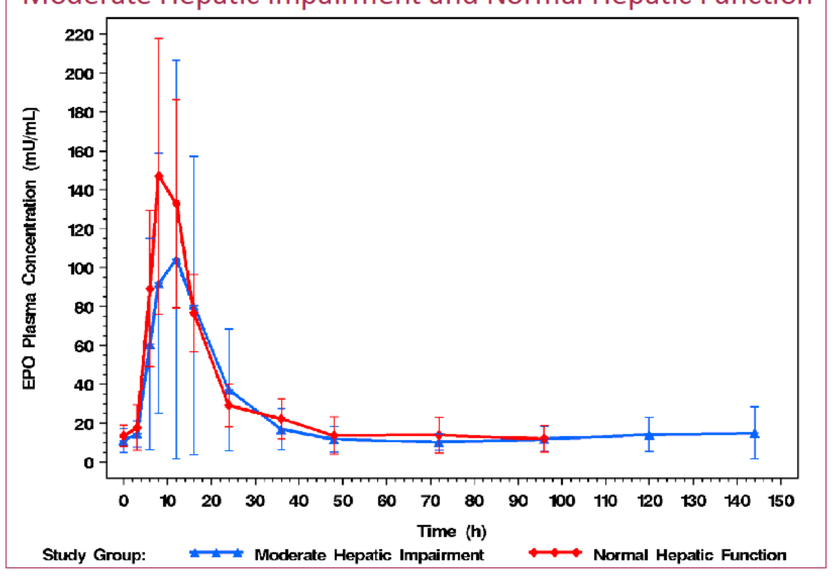



**Table 2:** Statistical Assessment for PD Parameters of EPO in Subjects with Moderate Hepatic Impairment and Normal Hepatic Function

| Parameter | Moderate Hepatic Impairment‡ (n=8) | Normal Hepatic Function‡ (n=8) | GMR (%) (90% CI) hepatic impaired/ normal |
|---|---|---|---|
| $E_{max}$ (mU/mL) | 114 (92%) | 155 (42%) | 56.4 (33.3, 95.7) |
| $AUC_{E,last}$ (mU·h/mL) | 3231 (61%) | 3009 (27%) | 100 (66.8, 151) |
| $t_{max,E}$ (h) | 10.0 (8.0 – 12) | 9.50 (8.0 - 16) | - |
| Baseline-Corrected | | | |
| $E_{max}$ (mU/mL) | 103 (98%) | 141 (47%) | 52.3 (29.0, 94.5) |
| $AUC_{E,last}$ (mU·h/mL) | 1635 (97%) | 1716 (29%) | 69.0 (29.3, 162) |

‡ Mean (CV%); Median (range) for $t_{max,E}$

### Tolerability

- A single 100 mg dose of roxadustat was generally well tolerated when administered in subjects with normal and moderate impaired hepatic function.
- In total, 2 treatment-emergent adverse events (TEAEs), neutropenia and headache, were both reported in subjects with moderate hepatic impairment. Both TEAEs were mild in severity and not considered clinically significant.
- TEAE of neutropenia was considered to be possibly related to study drug. Leukocyte and neutrophil count decreased after study drug administration and returned towards baseline values at end of study#.
- There were no relevant changes in vital signs, clinical laboratory analyses or ECG parameters.

# Leukocyte count (x10$^9$/L): 2.24 (screening) 3.26 (baseline), 1.77 (day 2), 1.67 (day 3), 1.70 (day 5), 1.84 (day 7), 2.45 (end of study); Neutrophil count (x10$^9$/L): 1.60 (screening), 2.30 (baseline), 1.11 (day 2), 1.10 (day 3), 1.10 (day 5), 1.30 (day 7), 1.80 (end of study).

## Conclusions

This study showed that subjects with moderate hepatic impairment exhibit only small changes in roxadustat exposure and pharmacodynamics relative to subjects with normal hepatic function. These small differences are not expected to be of clinical significance.

## References

1. Besarab A et al. American Society of Nephrology Kidney Week 2011 (Abstract # THPO364)

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