ROXADUSTAT (FG−4592), AN ORAL HYPOXIA INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITOR, DOES NOT AFFECT THE PHARMACOKINETICS OF WARFARIN IN HEALTHY SUBJECTS

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Introduction and Objectives

Roxadustat (FG−4592) is a hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), which is currently in phase 3 development for the treatment of anemia associated with chronic kidney disease (CKD).[1] Warfarin, a narrow therapeutic index drug, is often prescribed to treat co-existing cardiovascular diseases in the CKD population. S−warfarin is primarily metabolized by cytochrome P450 2C9,[2] for which roxadustat showed weak inhibitory potential in vitro.[3]

The objective of this study was to determine whether roxadustat affects the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin.

Methods

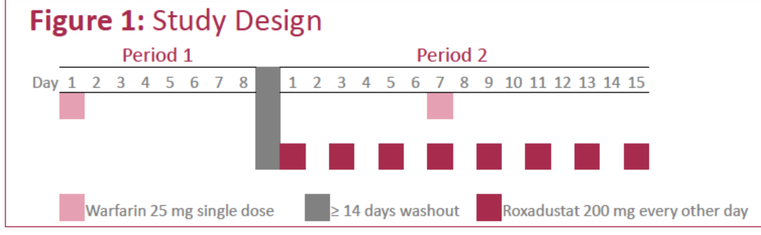
Subjects

- Healthy adult male or female subjects aged 18-55 y; body mass index (BMI) 18.5-30 kg/m^2.

Study Design

- Open−label, 2-period, one−sequence crossover study (Fig. 1).

Figure 1: Study Design



- Blood sampling: Warfarin PK: predose up to 168 h (Period 1) or 216 h postdose (Period 2). Unbound concentrations: 2, 8 and 24 h postdose in both periods; Roxadustat PK: predose on Days 1,3,5,11,13,15, and predose up to 48 h postdose on Day 7 of Period 2; Prothrombin Time (PT) and International Normalized Ratio (INR): predose up to 168 h (Period 1) or 216 h postdose (Period 2).
- Plasma concentrations of S- and R-warfarin and roxadustat were determined by validated LC-MS/MS.
- Safety and tolerability were assessed throughout the study.

Assessments

- Noncompartmental PK and PD parameters included: maximum observed plasma concentration (C_{max}); area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}); time of first occurrence of C_{max} (t_{max}); terminal elimination half-life ($t_{1/2}$); fraction unbound (fu); maximum observed PT (PT_{max}) and INR (INR_{max}); PT and INR AUC from time zero to the last measurable sample ($AUC_{PT,last}$ and $AUC_{INR,last}$); time of first occurrence of PT_{max} and INR_{max} (tPT_{max} and $tINR_{max}$).
- Geometric least-squares mean ratios (GMR) (with/without roxadustat) and associated 90% confidence intervals (CI) for log-transformed AUC_{inf} and C_{max} of total and unbound S- and R-warfarin, $AUC_{PT,last}$ $AUC_{INR,last}$, PT_{max} and INR_{max} were calculated using a linear mixed effects model controlling for treatment as fixed effect and subject as random effect.

Results

Subject Disposition

- 22 subjects received study treatment and 20 completed the study.
- Median age: 49 y (range 24-54); median BMI: 24.4 kg/m^2 (range 20.4-29.8); all White; 14 (64%) male.
- Reasons for discontinuation (n=1 each) were: adverse event (elevated transaminases) on Day 12 of Period 2, and positive drugs of abuse test before Period 2.

Results (continued)

Warfarin Pharmacokinetics

- PK profiles of S- and R-warfarin alone and in the presence of roxadustat were nearly identical (Fig. 2).
- The 90% CI of GMR of C_{max} and AUC_{inf} (with/without roxadustat) for total and unbound S- and R-warfarin were within the default 80 - 125% “no effect” interval (Table 1).

Figure 2: Mean (SD) Plasma Concentration-Time Profiles of S-Warfarin and R-Warfarin after Administration of Warfarin Alone and in Combination with Roxadustat

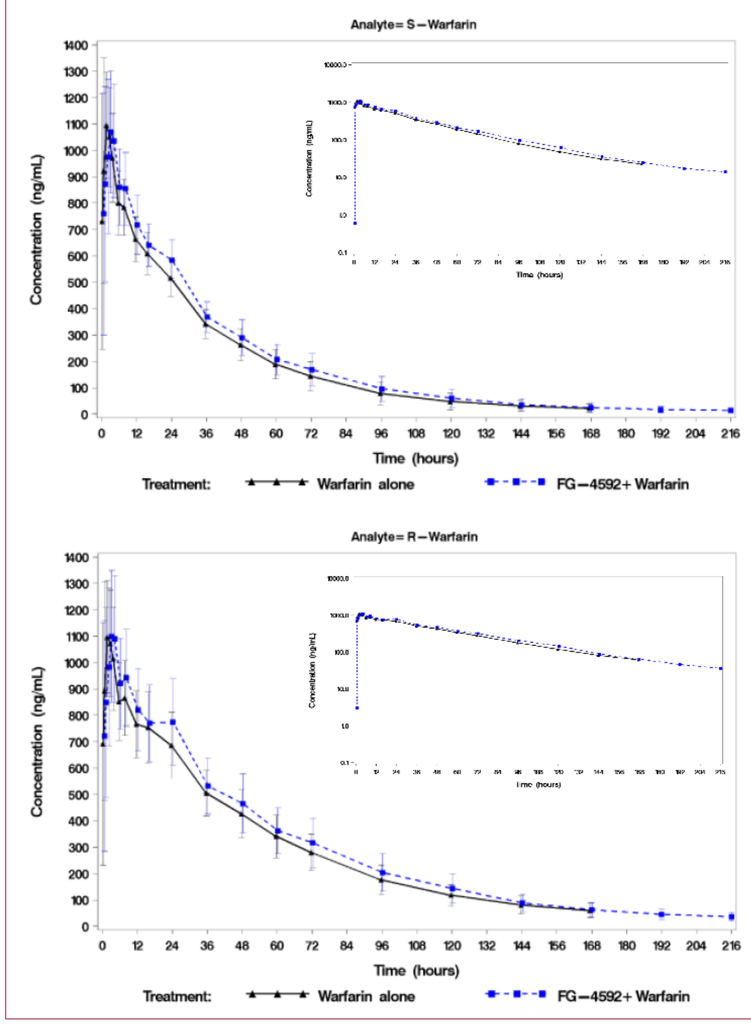


Table 1: Summary Statistics for PK Parameters of Warfarin Alone and in Combination with Roxadustat

Parameter	n	Warfarin Alone‡	n	Warfarin + Roxadustat‡	GMR (%) (90% CI) with/without Roxadustat
S−warfarin					
C_{max} (ng/mL)	22	1225 (281.7)	21	1201 (200.7)	99.1 (93.0, 105.6)
AUC_{inf} (ng·h/mL)	22	37150 (7200)	21	41340 (7646)	111.6 (108.5, 114.9)
$C_{max,u}$ (ng/mL)	22	9.44 (3.00)	21	9.18 (1.78)	99.4 (90.7, 109.0)
$AUC_{inf,u}$ (ng·h/mL)	22	284.2 (70.9)	21	314.8 (58.9)	111.9 (105.7, 118.5)
t_{max} (h)	22	2.00 (0.50 – 4.02)	21	2.02 (0.50 – 6.03)	-
$t_{1/2}$ (h)	22	34.0 (7.68)	21	39.9 (9.20)	-
fu (%)	22	0.766 (0.134)	21	0.763 (0.055)	-
R−warfarin					
C_{max} (ng/mL)	22	1195 (265.2)	21	1203 (204.3)	101.6 (96.7, 106.7)
AUC_{inf} (ng·h/mL)	22	57030 (12430)	21	63190 (15860)	110.8 (107.8, 113.8)
$C_{max,u}$ (ng/mL)	22	10.8 (3.27)	21	10.9 (1.89)	103.8 (96.3, 111.9)
$AUC_{inf,u}$ (ng·h/mL)	22	508.3 (124.7)	21	570.7 (131.5)	113.1 (107.6, 119.0)
t_{max} (h)	22	2.01 (0.50 – 4.02)	21	2.98 (0.50 – 8.05)	-
$t_{1/2}$ (h)	22	41.4 (7.28)	21	45.5 (7.37)	-
fu (%)	22	0.897 (0.153)	21	0.910 (0.067)	-

‡ Mean (SD); Median (range) for t_{max}

Subscript u denotes PK parameters for unbound drug.

Results (continued)

Warfarin Pharmacodynamics

- Compared with warfarin alone, concomitant warfarin and roxadustat dosing increased the average PD effect (PT and INR AUC_{last}) of warfarin by 24% (Figure 3, Table 2). The 90% CI of GMR of peak PT and INR were within the 80 - 125% interval.

Figure 3: Mean INR Profiles

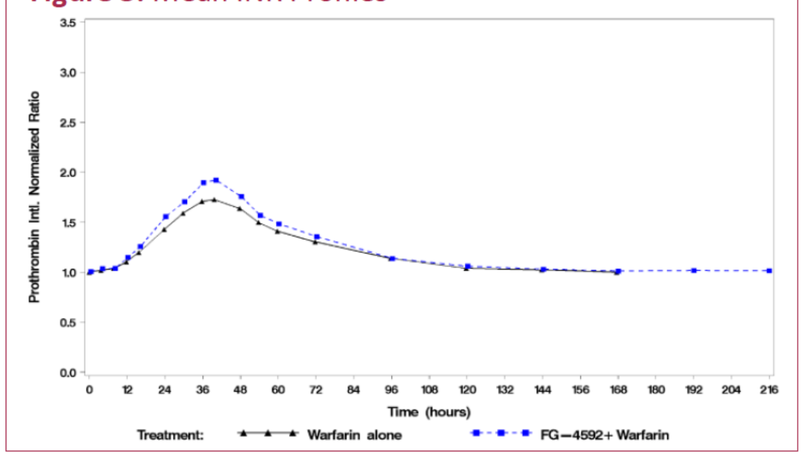


Table 2: Summary Statistics for PD Parameters of Warfarin Alone and in Combination with Roxadustat

Parameter	n	Warfarin Alone‡	n	Warfarin + Roxadustat‡	GMR (%) (90% CI) with/without Roxadustat
PT_{max} (sec)	22	18.8 (5.68)	21	20.7 (5.99)	109.3 (105.5, 113.3)
$AUC_{PT,last}$ (h·sec)	21	2202 (291.3)	20	2750 (370.4)	124.5 (119.4, 129.7)
INR_{max}	22	1.77 (0.545)	21	1.95 (0.574)	109.6 (105.7, 113.6)
$AUC_{INR,last}$ (h)	21	206.2 (27.81)	20	257.5 (35.1)	124.5 (119.4, 129.7)
tPT_{max} and $tINR_{max}$ (h)	22	36.0 (30.0 – 48.0)	21	40.0 (29.9 – 48.1)	-

‡ Mean (SD); Median (range) for t_{max}

Tolerability

- A single dose of warfarin was generally well tolerated when administered alone or in combination with roxadustat.
- Six subjects (27%) in Period 1 and 12 subjects (57%) in Period 2 reported at least one treatment-emergent adverse event (TEAE). Most TEAEs were mild in severity. There were no severe of serious TEAEs.
- Most common TEAEs were flatulence, vessel puncture site swelling and back pain.
- One subject experienced a TEAE (elevated transaminases) that led to withdrawal from the study.
- There were no relevant changes in vital signs or ECG parameters.

Conclusions

Co-administration of 200 mg roxadustat with a single dose of 25 mg warfarin did not result in clinically significant changes in the PK of S- or R-warfarin or the peak PD effect and caused only a small increase (24%) in the average PD effect (AUC) of warfarin.

Based on the lack of clinically significant PK interactions and the limited impact on warfarin PD, no dose adjustment of warfarin should be required when co-administered with roxadustat.

References

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3. Astellas data on file

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221--SP
H) Clinical Nephrology, CKD. H3) Anaemia in CKD 1-5.
Dorien Groenendaal-van de Meent
DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014