**Table S4.** Comparison of PK parameters between simulated and observed data for verification of the mechanistic kidney model of rivaroxaban in moderate to severe renal impairment.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Simulated (n=80) | | | | | | | Observed (n=8) | | | | | |
| 10 mg single dose, fasted (Kubitza et al. 2010)1  Moderate Renal Impairmenta | **AUC**  **(µg.h/L)** | **Cmax**  **(µg/L)** | | | **CLR**  **(L/h)** | | **AUC**  **(µg.h/L)** | | **Cmax**  **(µg/L)** | | | **CLR**  **(L/h)** | |
| Geometric mean | 2131 | 198 | | | 0.62 | | 2068 | | 206 | | | 0.7 | |
| CV (%) | 43 | 26 | | | 61 | | 33 | | 26 | | | 33 | |
| Ratio of simulated/observed | 1.03 | 0.96 | | | 0.89 | |  | |  | | |  | |
| Success criteria for ratio of simulated/observed | 0.62-1.62 | 0.68-1.47 | | 0.62-1.62 | |  | | | |  | | |  |
| Fold Change vs Healthyb | **AUC Fold Change (90% CI)** | | **CLR Fold Change (90% CI)** | | | **AUC Fold Change**c | | | | | **CLR Fold Change**d | | |
|  | 1.62 (1.45, 1.82) | | 0.30 (0.27, 0.35) | | | 1.52 | | | | | 0.29 | | |
| Success Criteria for Fold Change | 0.77-3.00 | | 0.15-0.57 | | |  | | | | |  | | |
|  | **Simulated (n=80)** | | | | | | | **Observed (n=8)** | | | | | |
| 10 mg single dose, fasted (Kubitza et al. 2010)1  Severe Renal Impairmenta | **AUC**  **(µg.h/L)** | **Cmax**  **(µg/L)** | | | **CLR**  **(L/h)** | | **AUC**  **(µg.h/L)** | | **Cmax**  **(µg/L)** | | | **CLR**  **(L/h)** | |
| Geometric mean | 2249 | 186 | | | 0.22 | | 2228 | | 232 | | | 0.5 | |
| CV (%) | 43 | 24 | | | 47 | | 37 | | 33 | | | 40 | |
| Ratio of simulated/observed | 1.00 | 0.80 | | | **0.44** | |  | |  | | |  | |
| Success criteria for ratio of simulated/observed | 0.58-1.72 | 0.68-1.47 | | 0.56-1.79 | |  | | | |  | | |  |
| Fold Change vs Healthyb | **AUC Fold Change (90% CI)** | | **CLR Fold Change (90% CI)** | | | **AUC Fold Change**c | | | | | **CLR Fold Change**d | | |
|  | 1.71 (1.53, 1.92) | | 0.11 (0.097, 0.12) | | | 1.64 | | | | | 0.21 | | |
| Success Criteria for Fold Change | 0.83-3.24 | | 0.11-0.41 | | |  | | | | |  | | |

AUC, area under the concentration-time curve from time zero to infinity; Cmax, maximum plasma concentration; CLR, renal clearance; CV, coefficient of variation

aHealthy controls (CrCL > 80mL/min), Mild renal impairment (defined as CrCL: 50-79 mL/min), moderate renal impairment (defined as CrCL: 30-49 mL/min), severe renal impairment (CrCL< 30 mL/min)

bPK parameters in healthy controls utilized for comparison were obtained from simulations where the mechanistic kidney model incorporating both P-gp and OAT-3 was used to simulate the plasma concentration-time profile of rivaroxaban after a single 10 mg dose administered under fasted conditions.

cObserved difference in AUCs between healthy and renal insufficiency group(s) were analyzed using log-transformed data by application of the student’s independent t-test or one-way ANOVA

dObserved CLR fold change = CLR (renal impairment) /CLR (healthy)

**Reference**

1. Kubitza, D. *et al.* Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br. J. Clin. Pharmacol.* **70**, 703–712 (2010).