**Supplement table 3: References used for chloroquine and hydroxychloroquine PBPK model validation.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | References | n | Subject | Ethnicity | Age (years) | Weight (kg) | Dose regimen | Sampling time |
| hydroxychloroquine | [1] | 5 | healthy volunteers | Caucasians | 22.6 (19-27) | 63.5 (55-68) | Infusion 310 mg hydroxychloroquine | 0, 0.25, 0.5 (end of infusion), 0.75, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 13, 24, 32, 48, 72, 96, 120,168 h. |
| [2] | 5 | healthy volunteers | Caucasians | No reported | No reported | Infusion 155 mg; Oral 155 mg hydroxychloroquine | Infusion Dose: 0, 0.25, 0.5(end of infusion), 0.75, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 13, 24, 32, 48, 72, 96, 120, 168 h  Oral Dose: 0, 0.75, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 13, 24, 32, 48, 72, 96, 120, 168 h. |
| [3] | 20 | healthy volunteers | Chinese | 18-40 | BMI:  19-24 kg/m2 | Oral 200 mg  hydroxychloroquine sulfate tablets | 0, 1, 2, 3, 4, 5, 7, 9, 12, 24, 48, 72, 120 h, day 10, day 20, day 40 and day 60. |
| chloroquine | [4] | 6 | children | Nigerians | 2- 6 | 7.6-27.2 | Oral 10 mg/kg chloroquine | 0.5, 1, 2, 4, 8 and  24 h and day3, 5, 7, 14, 21 and 28. |
| 5 | Nigerians | 2-3.5 | 6.1-8.6 | 0.5, 1, 2, 4, 8 and  24 h and day5, 7, 14 and 21. |
| [5] | 12 | adult | Finland | 21-28 | 65-80 | Oral 500 mg chloroquine phosphate | 0, 1.5, 3, 5, 8, 24, 48, 72, 144 and 192 h. |
| [6] | 11 | adult | Caucasians | 20-36 | 65-91 | chloroquine i.v and tablet 300 mg interval 56 days | 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 and 54 h and days 4, 5, 8, 12, 17, 24, 30 and 36 and occasionally up to day 60. |

**Supplement Table 4: Hydroxychloroquine and chloroquine PBPK model validation results by comparison between predicted and observed mean arithmetic AUC and Cmax.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Predicted AUC  (h∙ng/mL) | Observed  AUC  (h∙ng/mL) | AUC Ratio | Predicted Cmax  (ng/mL) | Observed  Cmax  (ng/mL) | Cmax Ratio | Reference |
| Hydroxychloroquine model validation | | | | | | |  |
| IV blood PK | 6937 | 5972 | 1.16 | 1204 | 1708 | 0.72 | [1] |
| IV blood PK | 6937 | 8156 | 0.85 | 1204 | 2188 | 0.55 | [2] |
| PO blood PK | 6401 | 5585 | 1.15 | 159 | 215 | 0.74 | [2] |
| PO plasma PK | 1117 | 753 | 1.48 | 28.6 | 34.3 | 0.83 | [3] |
| Chloroquine model validation | | | | | | |  |
| PO blood PK | 22041 | 25490 | 0.86 | 433 | 483 | 0.90 | [4] |
| IV blood PK | 13147 | 9230 | 1.42 | 168 | 134 | 1.21 | [5] |
| PO plasma PK | 4355 | 6110 | 0.71 | 84.1 | 76.0 | 1.11 | [6] |
| PO plasma PK | 6610 | 4990 | 1.32 | 83.7 | 73.0 | 1.15 | [6] |

**Supplement Table 5: The predicted pharmacokinetic parameters of chloroquine (regimen A) and hydroxychloroquine (regimen B, C, D, E, F) calculated by plasma concentration from Day 1 to Day 10.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PK parameters | Regimen A | Regimen B | Regimen C | Regimen D | Regimen E | Regimen F |
| Cmax (ng/mL) | 517 | 115 | 86.5 | 86.5 | 57.7 | 57.7 |
| AUC (h∙ng/mL) | 5837 | 994 | 745 | 745 | 497 | 497 |
| CL/F (L/h) | 52.5 | 641 | 641 | 641 | 641 | 641 |

**References**

[1] Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxy-chloroquine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1988. 26(3): 303-13.

[2] Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. Br J Clin Pharmacol. 1989. 27(6): 771-9.

[3] Fan HW, Ma ZX, Chen J, Yang XY, Cheng JL, Li YB. Pharmacokinetics and Bioequivalence Study of Hydroxychloroquine Sulfate Tablets in Chinese Healthy Volunteers by LC-MS/MS. Rheumatol Ther. 2015. 2(2): 183-195.

[4] Walker O, Dawodu AH, Salako LA, Alván G, Johnson AO. Single dose disposition of chloroquine in kwashiorkor and normal children--evidence for decreased absorption in kwashiorkor. Br J Clin Pharmacol. 1987. 23(4): 467-72.

[5] Gustafsson LL, Walker O, Alván G, et al. Disposition of chloroquine in man after single intravenous and oral doses. Br J Clin Pharmacol. 1983. 15(4): 471-9.

[6] Neuvonen PJ, Kivistö KT, Laine K, Pyykkö K. Prevention of chloroquine absorption by activated charcoal. Hum Exp Toxicol. 1992. 11(2): 117-20.