

**Table S4. Model Assumptions**

| Assumption   | Model  | Implications  | Mitigation strategy   |
|--|--|---|---|
| There is a linear relationship between HCQ concentrations and effect on viral decline.                                       | Clinical PK/PD model.                            | Extrapolation to much higher doses using a linear function may lead to overprediction of the drug effect.   | Doses used in simulations were capped at 600mg BID. Simulations were repeated using preclinical Emax PKPD relationships to understand if higher doses might offer clinical benefit. |
| The viral kinetics were modelled with a first-order growth and a first-order death rate, and a saturable maximal viral load. | Translational and Clinical PK/PD models.         | There is limited knowledge regarding the replication and death of SARS-Cov-2, especially in patients. Additionally, limited natural history data is publicly available.   | A sensitivity analysis was performed to understand how various natural history population profiles might impact interpretation of HCQ efficacy at different dose levels.            |
| HCQ pharmacokinetics are equivalent between (i) healthy or malaria infected patients and (ii) COVID-19 patients.             | Clinical PK simulations<br>Clinical PK/PD model. | There is no longitudinal PK data available from COVID-19 patients to develop a robust PK model, so population PK parameters derived from a pool of both healthy and malaria infected patients was used for PK simulations.                  | The PK model we employed from healthy and malaria infected populations predicted the sparse PK data in patients with COVID-19 well.   |
| The concentration QTc prolonging effect of CQ is the same or greater than that of HQC and the effect is linear.              | Clinical PK-QTc model                            | There are no models to describe the relationship between HCQ concentration and QTc prolongation. In order to explore how a higher HCQ dose might affect the QT interval we employed a model describing the relationship between CQ and QTc. | QTc prolongation must be studied carefully in this unique population group.   |
| The viral kinetics of SARS-CoV-1 and SARS-CoV-2 are similar.   | Translational PK/PD model                        | There is limited knowledge regarding the replication and death of SARS-Cov-2, especially in patients.   | SARS-CoV-1 and SARS-CoV-2 share an estimated 79.6% sequence homology, and therefore, it is not unreasonable to conclude that they may also share similar replication kinetics. (35) |