Table S1. Estimation of Fraction Metabolized (fm) by CYP3A4 with SDD Formulation Using Retrograde Function in Simcyp®. Dosing regimen: nirmatrelvir 300 mg single dose, ritonavir 100 mg three does at -12, 0, 12 h.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| fm | CLint,CYP3A4 (µL/min/pmol) | CLint,other,HLM (μL/min/mg protein) | Predicted/Observed Ratio | |
| **Cmax** | **AUCinf** |
| 0.80 | 0.139 | 4.30 | 0.89 | 0.74 |
| 0.85 | 0.148 | 3.23 | 0.92 | 0.87 |
| 0.99 | 0.173 | 0.215 | 1.05 | 1.72 |

**Table S2. Predicted versus Observed Exposure for Ritonavir in Paxlovid**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Dataset** | **Dosing Regimen** | **N** | **Observed** | | **Predicted** | | **Predicted/Observed** | |
| **Cmax (ng/mL)** | **AUCτ (ng.h/mL)** | **Cmax (ng/mL)** | **AUCτ (ng.h/mL)** | **Cmax** | **AUCτ** |
| #2 | Nirmatrelvir SDD 300 mg SD  Ritonavir 100 mg 3 Doses at -12, 0, 12 h | 12 | 1455 | 9209 | 869 | 6900 | 0.60 | 0.75 |
| #3 | Nirmatrelvir Tablet 300 mg SD  Ritonavir 100 mg 3 Doses at -12, 0, 12 h | 12 | 1542 | 9419 | 864 | 6862 | 0.56 | 0.73 |
| #5 | Nirmatrelvir Tablet 300 mg BID 5 days a  Ritonavir 100 mg BID 5 days a  Midazolam 2 mg SD on Day 5 | 12 | 1318 | 7279 | 1036 | 7967 | 0.79 | 1.09 |
| #6 | Nirmatrelvir Tablet 300 mg BID 2 days b  Ritonavir 100 mg BID 2 days b  Dabigatran Etexilate 75 mg SD on Day 5 | 24 | 1461 | 8394 | 934 | 7391 | 0.64 | 0.88 |

SD, single dose; SDD, spray-dried dispersion. a total 9 doses. b total 3 doses.

**Table S3. Simulations of Drug-Drug Interactions between Moderate and Weak CYP3A Inducers and Paxlovid**

|  |  |  |
| --- | --- | --- |
| **Dosing** | **Nirmatrelvir**  **AUCτR (90%CI)** | **Nirmatrelvir**  **CmaxR (90%CI)** |
| Efavirenz 600 mg (moderate CYP3A inducer) QD for 19 days  Paxlovid (300 mg nirmatrelvir and 100 mg ritonavir) BID on Days 15 to 19 | 0.95 (0.89, 1.02) | 0.97 (0.91, 1.02) |
| Rifampicin 10 mg (weak CYP3A inducer) QD for 19 days  Paxlovid (300 mg nirmatrelvir and 100 mg ritonavir) BID on Days 15 to 19 | 1.00 (0.94, 1.06) | 1.00 (0.95, 1.05) |

Trial design: 10 subjects x 10 trials, age 20-50, and female 50%. CI, confidence interval.

Figure S1. Ritonavir Exposure with Nirmatrelvir SDD Formulation in the Presence of Ritonavir (300 mg Nirmatrelvir and Three Doses of 100 mg Ritonavir at -12, 0, 12 h). Clinical data from NCT05263895 (relative bioavailability, Dataset #2, N=12). Human clinical data are presented as discrete points of mean value and standard deviation. Solid line in the middle is simulated mean concentration from the model. The two boundary lines represent 5th and 95th percentile.



Figure S2. Ritonavir Exposure with Nirmatrelvir Tablet in the Presence of Ritonavir (300 mg Nirmatrelvir Tablet and Three Doses of 100 mg Ritonavir at -12, 0, 12 h). Clinical data from NCT05263895 (relative bioavailability, Dataset #3, N=12). Human clinical data are presented as discrete points of mean value and standard deviation. Solid line in the middle is simulated mean concentration from the model. The two boundary lines represent 5th and 95th percentile.

**Figure S3. Ritonavir Exposure with Nirmatrelvir Tablet in the Presence of Ritonavir (300 mg Nirmatrelvir Tablet and 100 mg Ritonavir BID for 5 Days, 9 Doses Total). Clinical data from NCT05032950 (midazolam DDI, Dataset #5). Human clinical data are presented as discrete points of mean value and standard deviation. Solid line in the middle is simulated mean concentration from the model. The two boundary lines represent 5th and 95th percentile.**



Figure S4. Ritonavir Exposure with Nirmatrelvir Tablet in the Presence of Ritonavir (300 mg Nirmatrelvir Tablets and 100 mg Ritonavir BID for 2 Days, 3 Doses total). Clinical data from NCT05064800 (dabigatran etexilate DDI, Dataset #6). Human clinical data are presented as discrete points of mean value and standard deviation. Solid line in the middle is simulated mean concentration from the model. The two boundary lines represent 5th and 95th percentile.

