Supplementary Table 1: *Cytotoxicity and anti-SARS-CoV-2 activity of nirmatrelvir (NRM), EIDD-1931 (the active form of molnupiravir), remdesivir (RDV), sotrovimab (SOT), bebtelovimab (BEB), cilgavimab (CIL) and tixagevimab (TIX) in VERO-E6 cells. The antivirals were tested against the Wild Type B.1 strain and the BQ.1.1 Omicron variant. CC50: half-maximal toxic drug concentration; CC90: drug concentration that causes the death of 90% of cells; IC50: half-maximal inhibitor drug concentration; IC90: drug concentration inhibiting 90% of viral replication; SD: Standard Deviation; NA: Not Active.*

	CC_{50} µM Mean ± SD	**CC_{90} µM Mean ± SD**	**IC_{50} µM against B.1 Mean ± SD**	**IC_{90} µM against B.1 Mean ± SD**	**IC_{50} µM against BQ.1.1 Mean ± SD**	**IC_{90} µM against BQ.1.1 Mean ± SD**
NRM	40.7 ± 4.0	2.9 ± 0.2	0.1 ± 0.03	0.2 ± 0.1	0.1 ± 0.01	0.2 ± 0.01
EIDD-1931	43.3 ± 6.0	3.1 ± 0.4	2.4 ± 0.4	2.5 ± 0.1	1.6 ± 0.4	1.8 ± 0.7
RDV	17.2 ± 0.2	4.2 ± 0.6	0.06 ± 0.03	0.2 ± 0.05	0.03 ± 0.01	0.1 ± 0.01

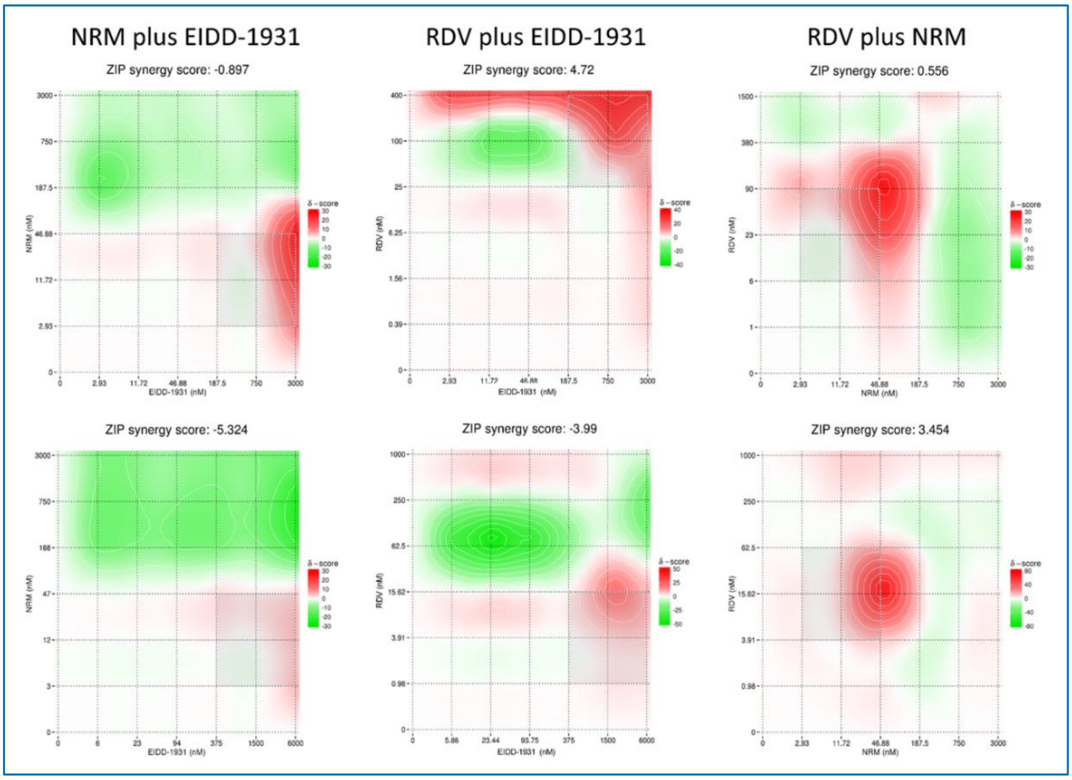
	CC_{50} ng/ml Mean ± SD	**CC_{90} ng/ml Mean ± SD**	**IC_{50} ng/ml against B.1 Mean ± SD**	**IC_{90} ng/ml against B.1 Mean ± SD**	**IC_{50} µM against BQ.1.1 Mean ± SD**	**IC_{90} µM against BQ.1.1 Mean ± SD**
SOT	>2400	>2400	813 ± 324	1718 ± 594	NA	NA
BEB	>60	>60	33 ± 7	89 ± 9	NA	NA
CIL	>360	>360	204 ±1354	1385 ± 862	NA	NA
TIX	>360	>360	68 ± 41	305 ± 71	NA	NA

Supplementary Table 2*. IC_{50} synergistic potency shift was measured in infected VERO E6 cells treated with 3 fixed drug concentrations of Compound 1 plus scalar dilution of Compound 2, for each combination. Fold shift values in Compound 2 IC_{50} were calculated as: IC_{50} [Compound 2 alone] / IC_{50} [Compound 1 + Compound 2]. DAA were tested against wild type B.1 SARS-COV-2 strain and BQ.1.1 variant while mAb/RDV combinations only against wild type B.1 SARS-COV-2 strain.*

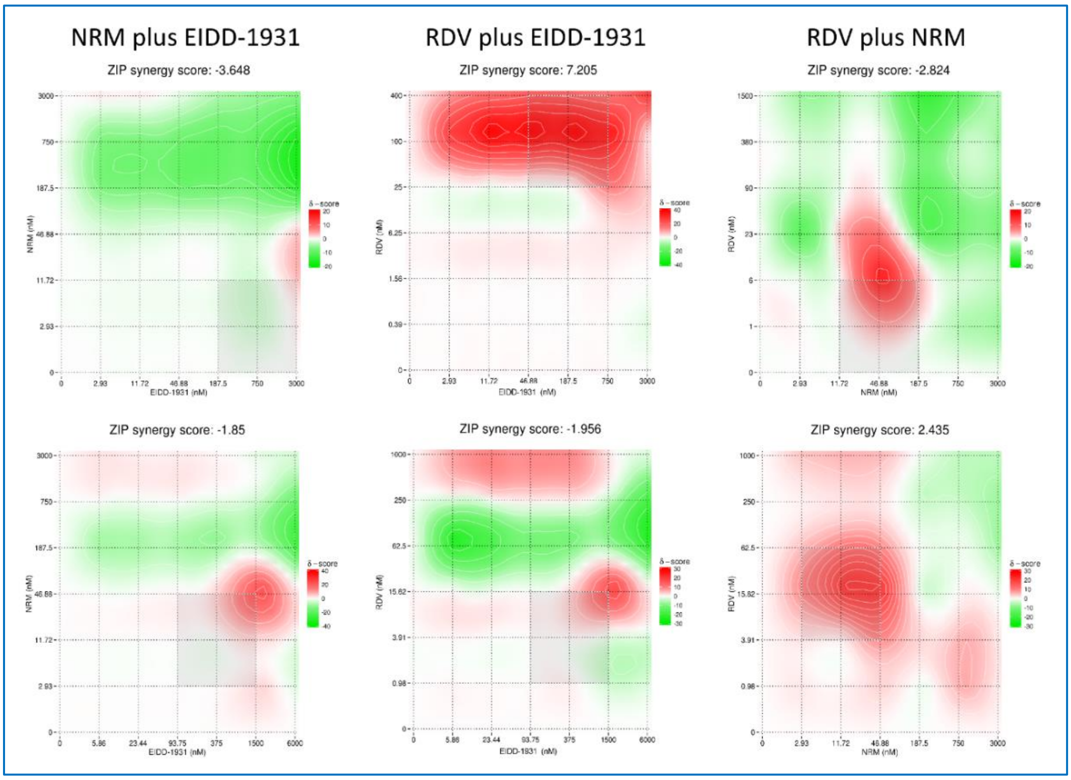
Against B.1			
EIDD-1931 IC_{50} Fold Reduction	**NRM 0.1 µM**	**NRM 0.05 µM**	**NRM 0.025 µM**
	88	11	1
	RDV 0.06 µM	**RDV 0.03 µM**	**RDV 0.015 µM**
	>26	26	2
NRM IC_{50} Fold Reduction	**RDV 0.06 µM**	**RDV 0.03 µM**	**RDV 0.015 µM**
	33	8	1
SOT IC_{50} Fold Reduction	**RDV 0.06 µM**	**RDV 0.03 µM**	**RDV 0.015 µM**
	4	2	2
BEB IC_{50} Fold Reduction	**RDV 0.06 µM**	**RDV 0.03 µM**	**RDV 0.015 µM**
	2	1	1
TIX IC_{50} Fold Reduction	**RDV 0.06 µM**	**RDV 0.03 µM**	**RDV 0.015 µM**
	3	2	1
Against BQ.1.1			
EIDD-1931 IC_{50} Fold Reduction	**NRM 0.1 µM**	**NRM 0.05 µM**	**NRM 0.025 µM**
	28	7	2
	RDV 0.06 µM	**RDV 0.03 µM**	**RDV 0.015 µM**
	>30	30	3
NRM IC_{50} Fold Reduction	**RDV 0.06 µM**	**RDV 0.03 µM**	**RDV 0.015 µM**
	140	14	2

Supplementary Figure 1: *Bi-dimensional (2D) synergy plots of antivirals against the two SARS-CoV-2 strains tested, generated by Synergy Finder 3.0 (*https://synergyfinder.fimm.fi/*) applying the ZIP model for each experiment performed. In A were reported the 2D plots of DAAs against the wild type B.1 virus, in supplementary B the 2D plots against the BQ.1.1 variant, and in C the 2D plots of RDV/mAb combinations against the wild type B.1 virus.*

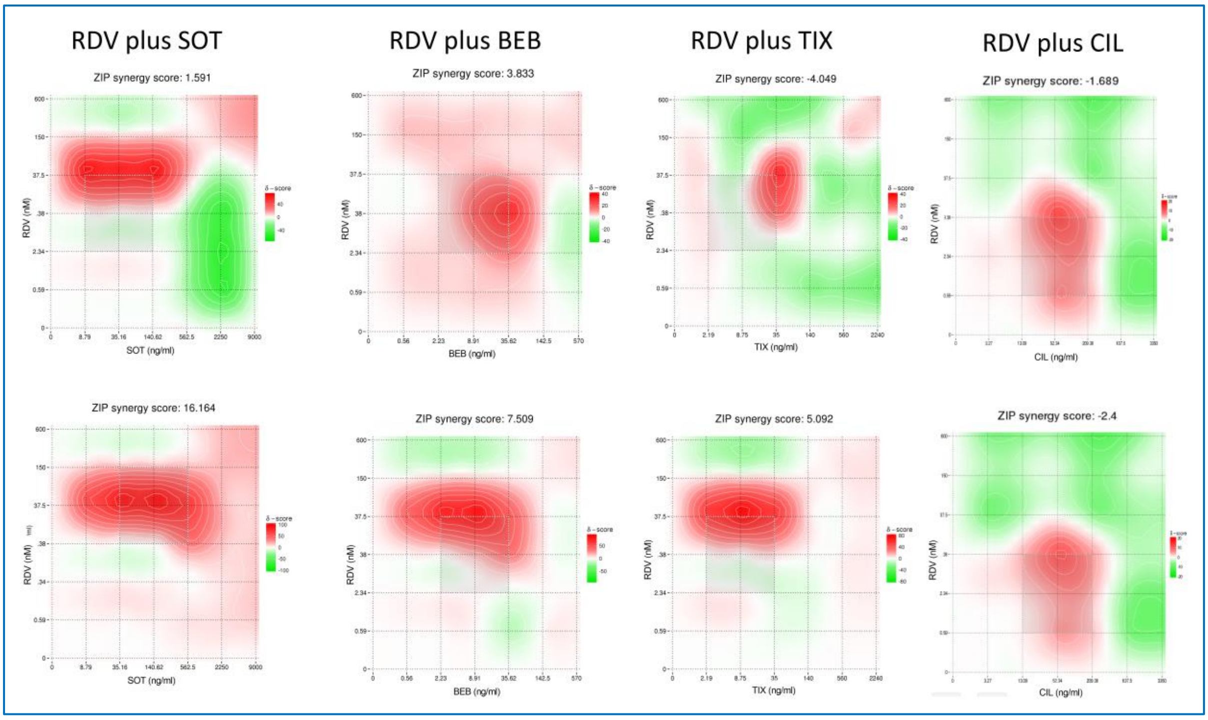
A



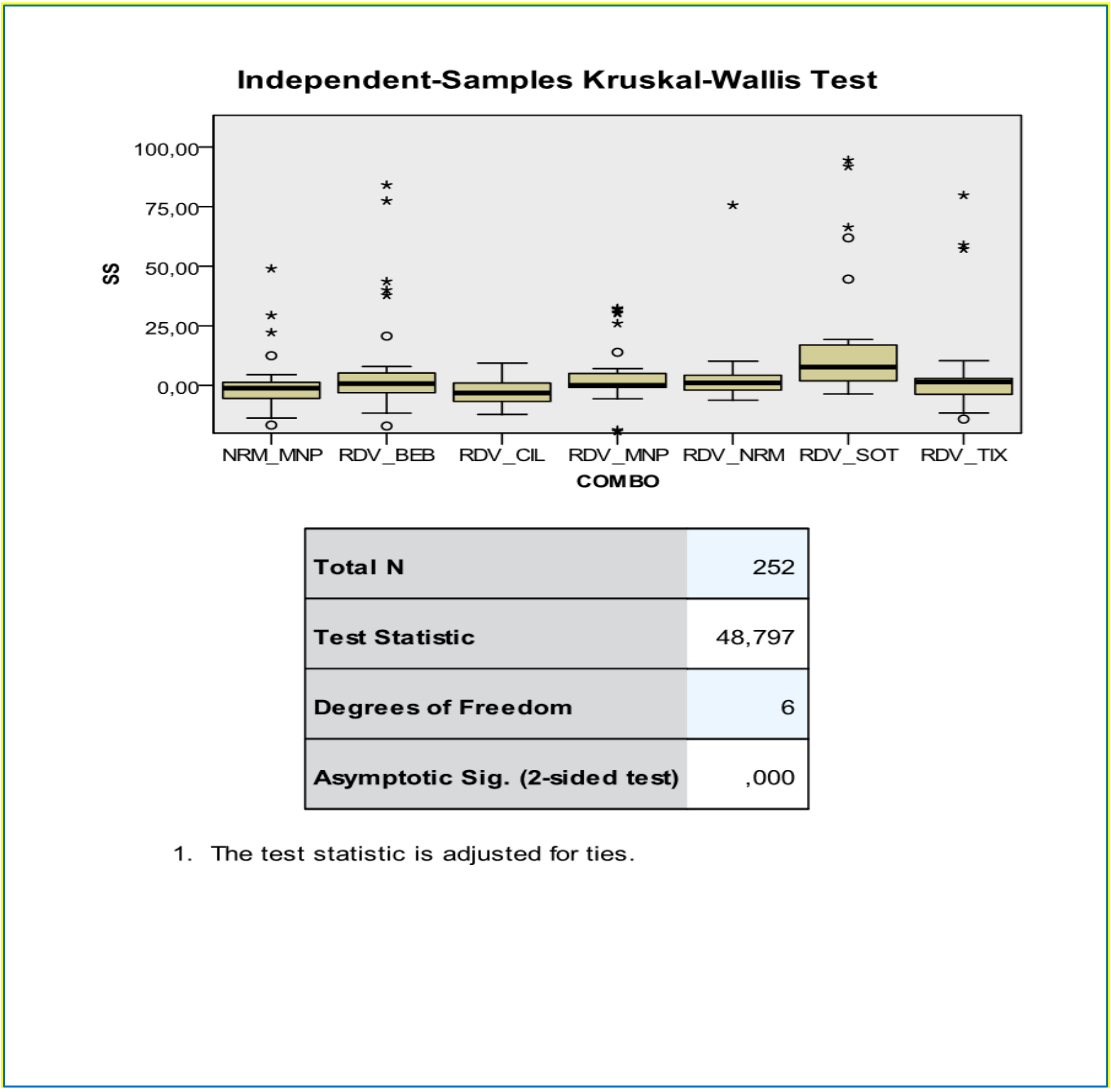
B



C



Supplementary Figure 2: *Overall combinatorial effects of the three DAA pairs as well as those of the three RDV/mAb groups were compared by the Kruskal-Wallis test followed by Mann-Whitney pairwise comparisons between groups. Statistical analysis were performed by SPSS version 20 (SPSS Inc, Chicago, IL USA).*



Independent-Samples Kruskal-Wallis Test

Total N	252
Test Statistic	48,797
Degrees of Freedom	6
Asymptotic Sig. (2-sided test)	,000

1. The test statistic is adjusted for ties.