

**Table S1. Treatment conditions and residual infectivity data from combination treatment assay.**

Treatment <sup>a</sup>	Concentration ( $\mu\text{M}$ ) <sup>b</sup>		Residual Infectivity (%) <sup>c</sup>		
	AMA	REM	AMA	REM	Combi
1	14.5	0.3	96	94	85
2	21.7	0.5	93	92	88
3	32.5	0.8	96	83	98
4	48.8	1.1	97	70	81
5	73.2	1.7	80	60	59
6	109.7	2.5	72	30	51
7	164.6	3.8	51	10	22
8	246.9	5.7	31	3	5
9	370.4	8.6	9	0	0
10	555.6	12.9	3	1	-1
Ratio <sup>d</sup>	43	1			

Treatment <sup>a</sup>	Concentration ( $\mu\text{M}$ ) <sup>b</sup>		Residual Infectivity (%) <sup>c</sup>		
	MEM	REM	MEM	REM	Combi
1	44.7	1.1	84	80	97
2	55.9	1.4	81	80	75
3	69.9	1.8	74	56	69
4	87.4	2.2	39	64	46
5	109.2	2.8	23	46	22
6	136.5	3.5	13	27	10
7	170.7	4.3	5	13	4
8	213.3	6.5	3	3	1
9	266.7	9.7	1	1	0
10	333.3	12.2	1	1	1
Ratio <sup>d</sup>	27	1			

Treatment <sup>a</sup>	Concentration ( $\mu\text{M}$ ) <sup>b</sup>		Residual Infectivity (%) <sup>c</sup>		
	RIM	REM	RIM	REM	Combi
1	5.5	0.3	96	94	101
2	8.2	0.5	101	92	92
3	12.4	0.8	86	83	87
4	18.5	1.1	74	70	62
5	27.8	1.7	44	60	40
6	41.7	2.5	26	30	17
7	62.6	3.8	7	10	0
8	93.8	5.7	1	3	-1
9	140.7	8.6	1	0	-2
10	211.1	12.9	1	1	0
Ratio <sup>d</sup>	16	1			

<sup>a</sup>Treatment, number of treatment condition and the specified concentrations of inhibitors. Infected cultures were treated with inhibitors either singly or in combination in antiviral treatment assays for analysis of interactions; results of these assays are shown in Figure 2.

<sup>b</sup> Concentration ( $\mu\text{M}$ ), concentrations of inhibitors, AMA, amantadine, MEM, memantine, RIM, rimantadine, REM, remdesivir.















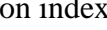


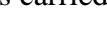

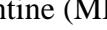




<sup>c</sup> Residual infectivity (%), calculated by relating the number of infected cells in treated cultures to the mean number of infected cells in infected-nontreated control cultures. Residual infectivity is given for single treatments with the specified inhibitors and the respective combination treatments (Combi) for each treatment condition.

<sup>d</sup> Ratio, for all inhibitor combinations a fixed concentration ratio was applied as specified.

**Table S2. Analysis of interactions of ion-channel inhibitors with remdesivir in Compusyn.**

	CI <sup>a</sup>				DRI <sup>b</sup>					
	Key Fa <sup>c</sup>		Experimental Fa <sup>b</sup>		Key Fa <sup>c</sup>			Experimental Fa <sup>d</sup>		
	Key Fa	CI	Exp. Fa	CI	Key Fa	AMA DRI	REM DRI	Exp. Fa	AMA DRI	REM DRI
<b>AMA+REM</b>	0.25	1.8	0.02	5.1	0.25	1.7	0.9	0.02	0.5	0.3
	0.5	1.8	0.12	1.3	0.5	1.7	0.9	0.12	2.1	1.2
	0.75	1.8	0.15	0.7	0.75	1.8	0.8	0.15	4.1	2.2
	0.9	1.8	0.19	2.2	0.9	1.9	0.8	0.19	1.3	0.7
			0.41	2.1				0.41	1.4	0.7
			0.49	2.6				0.49	1.2	0.6
			0.78	2.2				0.78	1.5	0.7
			0.95	1.5				0.95	2.3	1.0
			0.99	1.0				0.99	3.6	1.3
			0.99	1.5				0.99	2.4	0.9
<b>MEM+REM</b>	0.25	1.8	0.03	2.7	0.25	1.4	1.0	0.03	1.0	0.6
	0.5	1.7	0.25	1.6	0.5	1.4	1.0	0.25	1.5	1.1
	0.75	1.7	0.31	1.9	0.75	1.3	1.1	0.31	1.3	0.9
	0.9	1.6	0.54	1.7	0.9	1.3	1.2	0.54	1.4	1.1
			0.78	1.5				0.78	1.5	1.2
			0.9	1.4				0.9	1.6	1.4
			0.96	1.2				0.96	1.7	1.6
			0.99	1.2				0.99	1.7	1.7
			0.99	1.8				0.99	1.1	1.2
			0.99	2.2				0.99	0.9	0.9
<b>RIM+REM</b>	0.25	1.9	0.01	2.7	0.25	1.2	1.0	0.01	0.9	0.6
	0.5	1.8	0.08	1.8	0.5	1.2	1.1	0.08	1.3	1.0
	0.75	1.7	0.13	2.3	0.75	1.2	1.2	0.13	1.0	0.8
	0.9	1.6	0.38	1.7	0.9	1.2	1.3	0.38	1.2	1.1
			0.6	1.9				0.6	1.1	1.0
			0.83	1.7				0.83	1.2	1.2
			0.99	0.8				0.99	2.4	3
			0.99	1.1				0.99	1.6	2
			0.99	1.7				0.99	1.0	1.3
			0.99	2.6				0.99	0.7	0.9

CI	DRI
	 DRI ≥ 20
	 10 ≤ DRI < 20
	 5 ≤ DRI < 10
	 3 ≤ DRI < 5
	 1.5 ≤ DRI < 3
	 DRI < 1.5
	
	
	
	
	
	
	
	
	
	
	
	

<sup>a</sup> CI, Combination index values generated by analysis in CompuSyn of data from short-term treatment assays carried out for analysis of interactions of ion-channel inhibitors amantadine (AMA), memantine (MEM), rimantadine (RIM) and remdesivir (REM) (Figure 2 and Table S1). Graphical illustrations of these results are shown in Figure S5 B and C. CI are color-coded

according to the legend below the table and reflect the mode of interaction. In the range

$0.85 \leq CI < 0.9$  (slight synergism), no values were recorded.

<sup>b</sup> DRI, Drug reduction index values generated by CompuSyn analysis. DRI values are color-coded according to the legend below the table. Graphical illustrations of these results are shown in Figure S5 D.

<sup>c</sup> Key Fa, key fractional effects identical with key inhibition percentages (0.25, 0.5, 0.75 and 0.9).

<sup>d</sup> Experimental Fa, fractional effects identical with inhibition percentages achieved at experimental datapoints

**Table S3. Next generation sequencing of SARS-CoV-2 genomes from long-term treatment experiments.**

Nucleotide position <sup>a</sup>	Reference nucleotide <sup>b</sup>	Nucleotide change <sup>c</sup>	Frequency in non-treated day 5 (%) <sup>d</sup>	Frequency in Amantadine 3xEC50 day 5 (%) <sup>e</sup>	Frequency in Memantine 3xEC50 day 5 (%) <sup>e</sup>	Frequency in Rimantadine 3xEC50 day 5 (%) <sup>e</sup>	Frequency in Rimantadine 7xEC50 day 7 (%) <sup>e</sup>	Amino acid change <sup>f</sup>	SARS-CoV-2 protein <sup>g</sup>
2343	T	G	-	-	-	-	99.7	I513S	nsp2
3162	C	A	-	-	21.6	-	-	S148Y	nsp3
3482	G	A	-	-	52.0	-	-	G255R	nsp3
11522	T	G	-	-	-	98.6	-	F184V	nsp6
16534	A	G	5.5	-	-	-	-	S100G	nsp13
17368	A	G	5.2	-	-	-	-	M378V	nsp13
17964	G	T	6.3	-	-	-	-	M576I	nsp13
22487	A	G	52.6	89.8	23.1	99.5	-	K309E	S

<sup>a</sup>Nucleotide position relating to the SARS-CoV-2/human/Denmark/DK-AHH1/2020 genome

sequence (GenBank accession number MZ049597). Coding nucleotide changes occurring in at least one of the analyzed virus populations with  $\geq 5\%$  prevalence are listed.

<sup>b</sup>Nucleotide identity in the SARS-CoV-2/human/Denmark/DK-AHH1/2020 sequence.

<sup>c</sup>Changed nucleotide detected in cell culture derived virus.

<sup>d</sup>Frequency of the indicated nucleotide change in the genomes of the viral population in the nontreated culture on day 5 post infection. -, frequency of the indicated nucleotide change was below the limit of detection.

<sup>e</sup>Frequency of the indicated nucleotide change in the genomes in the viral populations in cultures subjected to the specified treatments at the given timepoint post infection and treatment initiation. -, frequency of the indicated nucleotide change was below the limit of detection

<sup>f</sup>Amino acid change encoded by the given nucleotide change. Position numbers relate to the respective protein of SARS-CoV-2/human/Denmark/DK-AHH1/2020.

<sup>g</sup>SARS-CoV-2 protein, where the given amino acid change is located.

**Table S4. Pharmacokinetics of adamantane derivatives**

<sup>a</sup>C<sub>max</sub>, maximum plasma concentrations (μM) of ion-channel inhibitors achieved in patients after

Inhibitor	C <sub>max</sub> (μM) <sup>a</sup>	C <sub>max</sub> /EC <sub>50</sub> <sup>b</sup>	Dose <sup>c</sup>	PPB <sup>d</sup>	Distribution to lungs <sup>e</sup>	References <sup>f</sup>
Amantadine	2.7	0.02/0.02/0.03	200mg single dose	67%	High	<a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s0161bl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s0161bl.pdf</a> , Bleidner, W. E., Harmon, J. B., Hewes, W. E., Lynes, T. E. & Hermann, E. C. ABSORPTION, DISTRIBUTION AND EXCRETION OF AMANTADINE HYDROCHLORIDE. <i>J. Pharmacol. Exp. Ther.</i> 150, (1965) doi: 10.1007/s12325-019-01044-y,
Memantine	0.1	0.001/0.001/0.001	20mg single dose	45%	High	Kuns, B., Rosnai, A. & Varghese, D. Memantine - StatPearls - NCBI Bookshelf. Memantine (2020)
Rimantadine	2.2	0.06/0.08/0.03	100mg/12hrs	40%	na	<a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019649s0151bl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019649s0151bl.pdf</a>

administration of specified dose(s). For rimantadine C<sub>max</sub> values were determined at steady state after multiple dosings.

<sup>b</sup>C<sub>max</sub>/EC<sub>50</sub>, peak plasma concentration (μM) relative to the EC<sub>50</sub> (μM) of inhibitor against SARS-CoV-2 determined in VeroE6, Huh7.5 and A549-hACE2 cells, respectively (Figure 1, Table 1).

<sup>c</sup>Dose, dosing scheme leading to the reported C<sub>max</sub> values. All doses are in accordance to recommended clinical dosings.

<sup>d</sup>PPB, plasma protein binding, % of compound bound to plasma proteins according to FDA reports.

<sup>e</sup>Distribution of inhibitor to pulmonary tissue relative to C<sub>max</sub>. na, data not available.

<sup>f</sup>References for listed C<sub>max</sub> values and distribution. Values were extracted from either FDA reports or if not available, values were extracted from publications on representative clinical studies