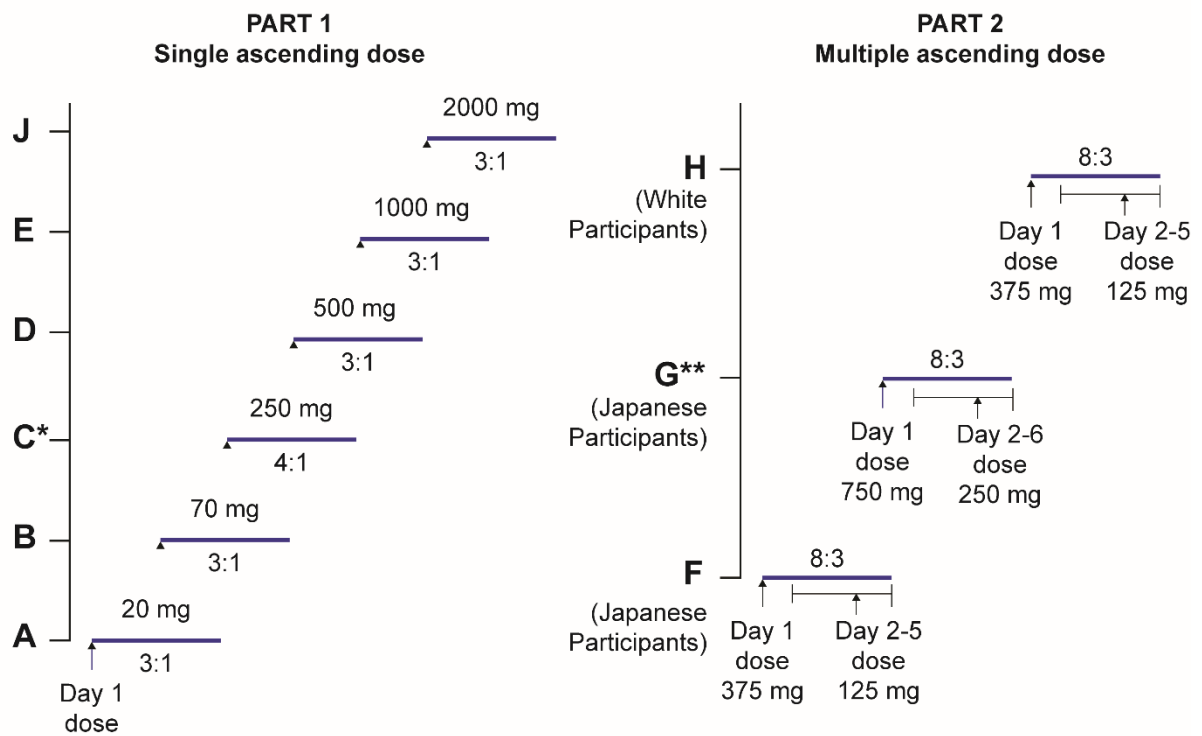


1 **Supplementary Material**

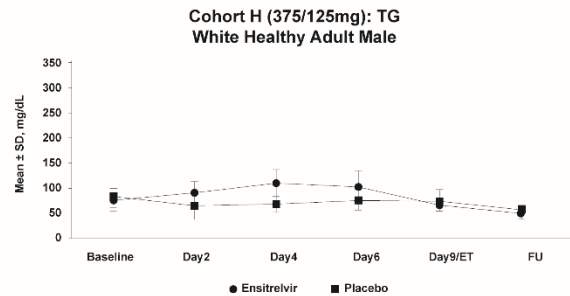
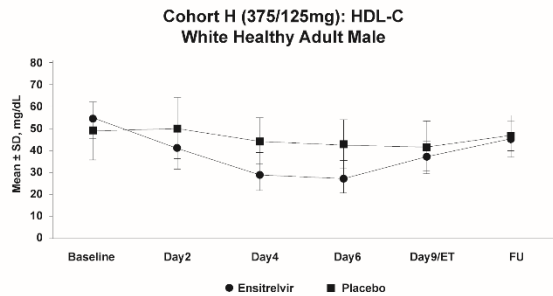
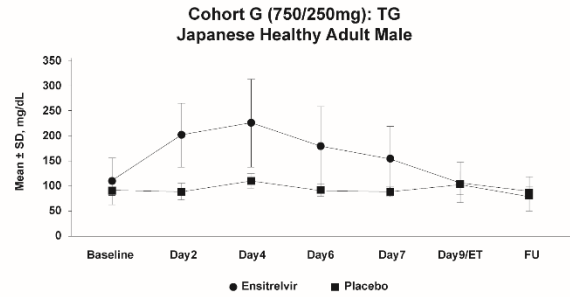
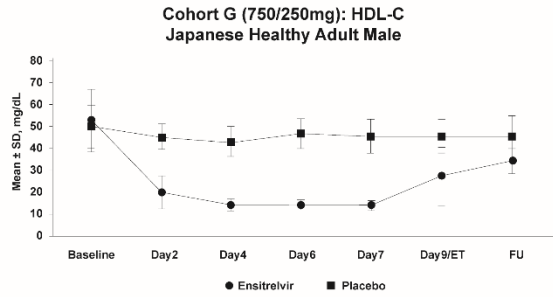
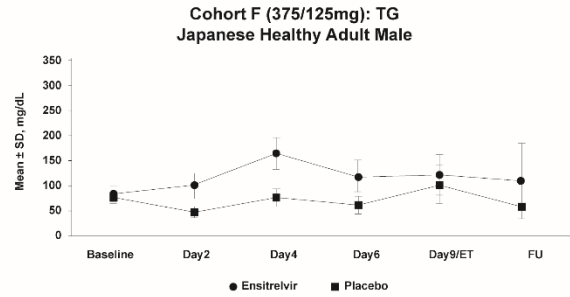
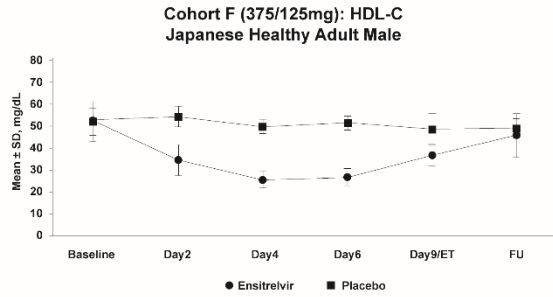
2 **Supplementary Figure S1: Study design**



3

4 \*In Part, Cohort C also involved the evaluation of the effect of food on the pharmacokinetics of ensitrelvir. In Part 2, Cohort  
5 G also involved the evaluation of the impact of ensitrelvir on the pharmacokinetics of midazolam on Day 2 and Day 6.

6 **Supplementary Figure S2: Change in HDL-C and TG levels in multiple-dose administration**



7

8 ET, early termination; FU, follow-up; HDL-C, High density lipoprotein – cholesterol; TG, triglycerides; 375/125 mg: once  
 9 daily multiple dose with 375 mg as the loading dose on Day 1 and 125 mg as the maintenance dose on Days 2 to 5; 725/250  
 10 mg: once daily multiple doses with 750 mg as the loading dose on Day 1 and 250 mg as the maintenance dose on Days 2 to 5  
 11 (or 6).

12 **Supplementary Table 1: Baseline demographics in the single dose administration part (Cohorts**  
 13 **A, B, C, D, E, and J)**

		Ensitrelvir							Placebo
		Cohort A	Cohort B	Cohort C1	Cohort C2	Cohort D	Cohort E	Cohort J	
		20 mg	70 mg	250 mg	250 mg	500 mg	1000 mg	2000 mg	
		N = 6	N = 6	N = 4	N = 4	N = 6	N = 6	N = 6	N = 12
Sex	Male N (%)	6 (100.0)	6 (100.0)	4 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)
	Age (Years)								
	N	6	6	4	4	6	6	6	12
	Mean (SD)	28.3 (5.7)	24.0 (4.2)	27.3 (4.1)	27.5 (4.1)	22.3 (2.7)	32.8 (9.9)	29.8 (5.5)	29.3 (5.4)
	Min	20	20	22	23	20	24	23	20
	Median	28.0	22.5	28.0	27.0	21.5	30.5	31.0	29.0
	Max	36	31	31	33	26	52	37	37
Height (cm)	N	6	6	4	4	6	6	6	12
	Mean (SD)	168.98 (4.12)	172.33 (4.07)	174.78 (1.83)	172.80 (5.86)	171.98 (6.65)	171.00 (6.16)	173.82 (6.03)	170.23 (3.42)
	Min	163.7	168.3	173.3	164.3	165.4	164.2	163.6	165.0
	Median	169.95	170.95	174.20	175.10	169.10	170.20	174.10	169.95
	Max	173.0	178.7	177.4	176.7	182.5	180.5	181.6	177.1

		Ensitrelvir						Placebo	
		Cohort A	Cohort B	Cohort C1	Cohort C2	Cohort D	Cohort E	Cohort J	
		20 mg	70 mg	250 mg	250 mg	500 mg	1000 mg	2000 mg	N = 12
		N = 6	N = 6	N = 4	N = 4	N = 6	N = 6	N = 6	
Weight (kg)	N	6	6	4	4	6	6	6	12
	Mean (SD)	61.20 (5.16)	64.10 (6.11)	66.20 (5.85)	67.03 (2.52)	62.28 (7.39)	66.50 (11.15)	63.80 (4.56)	61.84 (5.05)
	Min	53.5	55.6	58.8	64.5	52.5	54.4	55.8	51.9
	Median	62.75	63.85	66.70	66.60	61.65	67.35	65.65	62.55
	Max	67.1	73.7	72.6	70.4	71.7	83.8	68.0	69.6
BMI (kg/m <sup>2</sup> )	N	6	6	4	4	6	6	6	12
	Mean (SD)	21.33 (1.65)	21.33 (1.86)	21.30 (1.78)	22.38 (0.76)	20.75 (2.01)	22.55 (2.75)	20.83 (1.04)	21.22 (1.58)
	Min	19.2	19.0	18.8	21.7	18.9	19.5	19.3	18.8
	Median	21.40	21.00	21.80	22.20	20.10	22.10	21.00	21.55
	Max	23.8	23.9	22.8	23.4	23.9	26.1	22.0	24.0
Race	Asian N (%)	6 (100.0)	6 (100.0)	4 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)
Substance usage (alcohol)	Yes	3 (50.0)	3 (50.0)	1 (25.0)	0	4 (66.7)	0	2 (33.3)	3 (25.0)
	No	3 (50.0)	3 (50.0)	3 (75.0)	4 (100.0)	2 (33.3)	6 (100.0)	4 (66.7)	9 (75.0)
Substance usage (tobacco)	Yes	0	0	0	0	0	0	0	0
	No	6 (100.0)	6 (100.0)	4 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)
Substance usage (caffeine)	Yes	4 (66.7)	4 (66.7)	3 (75.0)	0	3 (50.0)	0	4 (66.7)	8 (66.7)
	No	2 (33.3)	2 (33.3)	1 (25.0)	4 (100.0)	3 (50.0)	6 (100.0)	2 (33.3)	4 (33.3)
SARS-CoV-2 test	Negative	6 (100.0)	6 (100.0)	4 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)

14 "Placebo" includes all participants given placebo in all cohorts in Part 1. The last values taken before first administration were

15 used if there were multiple results. Participants of Cohort C1 received administration in the fasted state on Period 1 and after

16 a meal on Period 2. Participants of Cohort C2 received administration after a meal on Period 1 and in the fasted state on Period

17 2.

18 BMI, Body Mass Index; Max, Maximum; Min, Minimum; N, Number of participants; SARS-CoV-2, Severe Acute Respiratory

19 Syndrome Coronavirus 2; SD, Standard Deviation.

## 20 **Supplementary Table 2: Baseline demographics in the multiple-dose administration**

### 21 **part (Cohorts F, G, and H)**

		Ensitrelvir			Placebo		
		Cohort F	Cohort G	Cohort H	Cohort F	Cohort G	Cohort H
		375/125 mg	750/250 mg + Midazolam	375/125 mg		Placebo + Midazolam	
		N = 8	N = 8	N = 8	N = 3	N = 3	N = 3
Sex	Male N (%)	8 (100.0)	8 (100.0)	8 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)
Age (Years) (informed consent obtained)	N	8	8	8	3	3	3
	Mean (SD)	33.4 (5.2)	29.4 (7.3)	36.0 (6.9)	32.3 (1.5)	30.0 (7.9)	34.0 (6.9)
	Min	25	20	26	31	21	26

		Ensitrelvir			Placebo		
		Cohort F 375/125 mg	Cohort G 750/250 mg + Midazolam	Cohort H 375/125 mg	Cohort F	Cohort G Placebo + Midazolam	Cohort H
		N = 8	N = 8	N = 8	N = 3	N = 3	N = 3
Height (cm)	Median	34.0	29.0	34.5	32.0	33.0	38.0
	Max	39	40	45	34	36	38
	N	8	8	8	3	3	3
	Mean (SD)	171.65 (5.12)	171.00 (8.72)	181.01 (9.58)	176.13 (1.52)	172.53 (4.39)	181.63 (7.28)
	Min	165.6	161.9	167.9	174.5	169.9	174.0
Weight (kg)	Median	171.70	168.50	179.15	176.40	170.10	182.40
	Max	181.9	186.0	197.6	177.5	177.6	188.5
	N	8	8	8	3	3	3
	Mean (SD)	66.58 (7.08)	68.03 (11.91)	74.68 (8.32)	67.03 (6.68)	62.57 (2.05)	81.13 (3.23)
	Min	60.4	55.9	62.0	60.0	60.3	78.2
BMI (kg/m <sup>2</sup> )	Median	63.50	65.80	75.05	67.80	63.10	80.60
	Max	80.2	85.0	87.2	73.3	64.3	84.6
	N	8	8	8	3	3	3
	Mean (SD)	22.36 (1.38)	22.99 (2.54)	22.83 (2.91)	21.70 (1.70)	21.10 (1.35)	24.40 (2.00)
	Min	21.0	19.7	20.0	20.0	19.8	22.1
Race	Median	22.00	23.95	22.35	21.70	21.00	25.40
	Max	24.7	25.5	27.1	23.4	22.5	25.7
	Asian N (%)	8 (100.0)	8 (100.0)	0	3 (100.0)	3 (100.0)	0
Substance usage (alcohol)	White N (%)	0	0	8 (100.0)	0	0	3 (100.0)
	Yes	0	0	0	0	0	0
Substance usage (tobacco)	No	8 (100.0)	8 (100.0)	8 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)
	Yes	0	0	0	0	0	0
SARS-CoV- 2 test	No	8 (100.0)	8 (100.0)	8 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)
	Negative	8 (100.0)	8 (100.0)	8 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)
	Positive	0	0	0	0	0	0

22 The last values taken before first administration were used if there were multiple results. Participants in Cohort F and G were  
23 Japanese healthy adult males. Participants in Cohort H were White healthy adult males. 375/125 mg: once daily multiple dose  
24 with 375 mg as the loading dose on Day 1 and 125 mg as the maintenance dose on Days 2 to 5; 725/250 mg: once daily  
25 multiple doses with 750 mg as the loading dose on Day 1 and 250 mg as the maintenance dose on Days 2 to 6.

26 BMI, Body Mass Index; Max, Maximum; Min, Minimum; N, Number of participants; SARS-CoV-2, Severe Acute Respiratory  
27 Syndrome Coronavirus 2; SD, Standard Deviation.

28 **Supplementary Table 3: Blood lipid profiling of participants over the study period in the single**  
29 **dose administration part (Cohorts A, B, C, D, E, and J)**

Parameter (unit)	Time point [Cohort C, Period 2]	Statistic	Ensitrelvir						Placebo N = 12
			Cohort A 20 mg N = 6	Cohort B 70 mg N = 6	Cohort C fasted state 250 mg N = 8	Cohort D 500 mg N = 6	Cohort E 1000 mg N = 6	Cohort J 2000 mg N = 6	
Cholesterol (mmol/L)	Baseline	n	6	6	8	6	6	6	12
		Mean (SD)	4.1635 (0.4177)	4.0987 (0.4716)	4.1053 (0.6235)	4.2838 (0.5674)	4.1332 (0.5434)	4.4608 (0.8547)	4.6333 (0.6946)
		Min	3.724	3.439	2.948	3.491	3.310	3.414	3.362
		Median	4.0730	4.0470	4.1505	4.2795	4.2410	4.2280	4.6290
	Day 2 [Day 16]	Max	4.810	4.707	4.758	5.094	4.758	5.508	5.870
		n	6	6	8	6	6	6	12
		Mean (SD)	4.2842 (0.4263)	4.1463 (0.5889)	3.8918 (0.6153)	3.9005 (0.5669)	3.5257 (0.4598)	3.9952 (0.9013)	4.7388 (0.7924)
		Min	3.905	3.388	2.870	3.155	2.767	2.870	3.414
	Day 4 [Day 18]	Median	4.1245	4.0860	3.9305	3.8660	3.6205	3.7625	4.7320
		Max	4.939	5.043	4.655	4.629	3.957	5.198	6.310
		n	6	6	8	6	6	6	12
		Mean (SD)	4.2668 (0.4032)	4.0515 (0.7018)	3.9695 (0.4928)	3.8273 (0.5428)	3.2498 (0.5322)	3.4133 (0.7824)	4.6008 (0.8016)
	Day 7 [Day 21]/ Early termination	Min	3.750	3.129	3.388	3.103	2.302	2.379	3.155
		Median	4.3055	3.9305	3.9825	4.0470	3.3230	3.3615	4.4735
		Max	4.810	5.017	4.577	4.293	3.905	4.422	6.413
		n	6	6	8	6	6	6	12
	Follow up	Mean (SD)	4.1290 (0.4327)	3.8145 (0.7363)	4.0019 (0.5499)	3.8103 (0.5863)	3.7628 (0.5824)	3.9437 (0.7807)	4.4458 (0.8482)
		Min	3.646	2.974	3.103	3.129	2.664	3.077	2.948
		Median	4.1505	3.5815	4.0340	3.8535	3.9180	3.7235	4.3315
		Max	4.707	4.888	4.810	4.681	4.396	5.069	6.310
Follow up	n	6	6	4	6	6	6	11	
	Mean (SD)	3.9048 (0.2727)	3.7368 (0.6184)	3.9760 (0.7375)	3.6505 (0.4573)	3.7410 (0.5172)	3.7112 (0.6677)	4.2294 (0.7944)	
	Min	3.465	2.922	2.896	2.974	2.741	3.026	3.129	
	Median	3.9695	3.7110	4.2670	3.6460	3.9435	3.5430	3.9570	
Follow up	Max	4.215	4.707	4.474	4.293	4.138	4.526	5.741	
	n	6	6	8	6	6	6	12	
	Mean (SD)	460.0 (46.0)	436.7 (46.8)	486.3 (76.1)	546.7 (127.9)	413.3 (80.7)	543.3 (82.6)	567.5 (99.8)	
	Min	400	370	370	380	300	420	450	
Day 2 [Day 16]	Median	470.0	445.0	510.0	540.0	425.0	535.0	530.0	
	Max	510	480	570	710	530	640	750	
	n	6	6	8	6	6	6	12	
	Mean (SD)	458.3 (47.9)	413.3 (42.7)	376.3 (81.9)	330.0 (106.6)	166.7 (45.5)	225.0 (76.6)	569.2 (99.6)	
Day 4 [Day 18]	Min	390	360	220	200	100	150	450	
	Median	465.0	430.0	380.0	325.0	175.0	200.0	530.0	
	Max	520	450	470	460	220	330	770	
	n	6	6	8	6	6	6	12	
Day 7 [Day 21]/ Early termination	Mean (SD)	446.7 (63.1)	411.7 (52.3)	401.3 (66.4)	340.0 (74.8)	180.0 (52.5)	171.7 (55.6)	538.3 (94.9)	
	Min	370	340	300	230	140	120	440	
	Median	450.0	420.0	390.0	340.0	165.0	155.0	510.0	
	Max	510	470	480	440	280	280	730	
Day 7 [Day 21]/ Early termination	n	6	6	8	6	6	6	12	
	Mean (SD)	440.0 (66.9)	396.7 (60.2)	438.8 (76.6)	421.7 (83.8)	303.3 (61.5)	253.3 (105.0)	531.7 (107.7)	

	Min	370	320	330	280	210	40	410	
	Median	445.0	400.0	445.0	440.0	305.0	295.0	505.0	
	Max	510	480	530	500	400	310	750	
LDL-C (mg/L)	Follow up	n	6	6	4	6	6	11	
		Mean (SD)	445.0 (70.1)	420.0 (55.1)	445.0 (113.9)	450.0 (85.1)	343.3 (47.2)	405.0 (45.9)	533.6 (113.2)
		Min	370	350	340	320	260	360	410
		Median	440.0	435.0	425.0	470.0	350.0	395.0	500.0
		Max	530	490	590	540	400	490	760
	Baseline	n	6	8	8	6	6	6	12
		Mean (SD)	993.3 (142.4)	995.0 (194.6)	900.0 (199.3)	990.0 (228.7)	986.7 (175.3)	1051.7 (296.1)	1052.5 (263.9)
		Min	850	770	540	710	690	750	630
		Median	970.0	920.0	865.0	945.0	1015.0	995.0	1020.0
		Max	1230	1310	1150	1360	1170	1410	1620
		Day 2 [Day 16]	n	6	6	8	6	6	12
		Mean (SD)	1048.3 (164.1)	1041.7 (241.5)	916.3 (179.2)	951.7 (219.6)	840.0 (141.8)	901.7 (268.8)	1112.5 (317.2)
	Min	900	790	580	700	580	630	610	
	Median	1015.0	965.0	885.0	925.0	880.0	815.0	1075.0	
	Max	1310	1470	1150	1250	970	1250	1910	
	Day 4 [Day 18]	n	6	6	8	6	6	12	
	Mean (SD)	1026.7 (152.3)	946.7 (254.0)	942.5 (140.8)	950.0 (219.1)	800.0 (159.1)	865.0 (239.7)	1047.5 (320.9)	
	Min	840	670	740	620	540	550	550	
	Median	1050.0	880.0	930.0	985.0	875.0	870.0	1000.0	
	Max	1190	1360	1160	1200	940	1200	1900	
	Day 7 [Day 21]/ Early termination	n	6	6	8	6	6	12	
	Mean (SD)	966.7 (150.6)	881.7 (293.5)	923.8 (136.4)	928.3 (263.5)	1003.3 (198.3)	1135.0 (327.0)	1015.8 (346.6)	
	Min	770	620	710	610	620	820	500	
	Median	1015.0	790.0	900.0	900.0	1080.0	1020.0	955.0	
	Max	1110	1370	1130	1350	1160	1610	1900	
Triglyceride (mmol/L)	Follow up	n	6	6	4	6	6	11	
		Mean (SD)	923.3 (104.6)	873.3 (242.9)	977.5 (213.0)	843.3 (216.1)	988.3 (155.1)	951.7 (249.0)	956.4 (299.2)
		Min	790	630	680	630	680	700	580
		Median	915.0	805.0	1030.0	795.0	1035.0	865.0	920.0
		Max	1080	1320	1170	1170	1100	1260	1490
	Baseline	n	6	6	8	6	6	6	12
		Mean (SD)	0.8825 (0.2807)	1.0330 (0.3537)	0.9596 (0.4428)	0.7507 (0.1445)	1.0275 (0.3223)	0.9975 (0.4064)	0.8702 (0.3224)
		Min	0.644	0.485	0.474	0.632	0.565	0.542	0.440
		Median	0.7730	1.0615	0.8245	0.7055	1.0840	1.0220	0.7730
		Max	1.321	1.479	1.863	1.016	1.332	1.479	1.671
		Day 2 [Day 16]	n	6	6	8	6	6	12
		Mean (SD)	1.0032 (0.2053)	1.1478 (0.2935)	1.3053 (0.6212)	1.2928 (0.2879)	2.3427 (0.6155)	2.0737 (0.5253)	0.9314 (0.2873)
	Min	0.700	0.711	0.598	1.039	1.456	1.524	0.463	
	Median	1.0165	1.0895	1.1345	1.1740	2.2295	1.9475	0.8525	
	Max	1.310	1.547	2.506	1.818	3.105	2.789	1.603	
	Day 4 [Day 18]	n	6	6	8	6	6	12	

	Mean (SD)	1.3643 (0.2213)	1.4170 (0.5431)	1.2235 (0.3569)	1.1327 (0.1334)	1.9683 (0.5250)	1.7668 (0.4684)	1.2945 (0.4778)
	Min	1.084	0.948	0.892	0.937	1.321	1.073	0.745
	Median	1.2985	1.3270	1.0670	1.1400	1.8855	1.8120	1.1400
	Max	1.671	2.427	1.795	1.276	2.755	2.303	2.427
Day 7 [Day 21]/ Early termination	n	6	6	8	6	6	6	12
	Mean (SD)	1.3852 (0.2059)	1.4393 (0.6236)	1.0571 (0.4382)	0.9937 (0.1403)	1.2210 (0.5146)	0.7867 (0.1677)	1.1950 (0.3927)
	Min	1.039	0.858	0.790	0.779	0.632	0.508	0.655
	Median	1.4285	1.2810	0.8470	0.9770	1.1570	0.8130	1.1745
	Max	1.581	2.608	2.010	1.174	1.818	0.971	1.897
Follow up	n	6	6	4	6	6	6	11
	Mean (SD)	0.7037 (0.1371)	0.8882 (0.4558)	0.6295 (0.1096)	0.5627 (0.0611)	0.7565 (0.3775)	0.4255 (0.1538)	0.8015 (0.7116)
	Min	0.587	0.305	0.542	0.463	0.463	0.294	0.327
	Median	0.6605	0.7620	0.5985	0.5700	0.5480	0.3615	0.5870
	Max	0.948	1.626	0.779	0.632	1.264	0.689	2.845

30 "Placebo" includes all participants given placebo in all cohorts in Part 1. The last values taken before first administration were  
31 used if there were multiple results. Four participants of Cohort C received administration in the fasted state on Period 1 and  
32 after a meal on Period 2. The other four participants of Cohort C received administration after meal on Period 1 and in the  
33 fasted state on Period 2 (Day 16, 18 and 21).  
34 HDL-C, high density lipoprotein-Cholesterol; LDL-C, low density lipoprotein-Cholesterol; Max, Maximum; Min, Minimum;  
35 N, Number of participants; SD, Standard Deviation.

#### 36 **Supplementary Table 4: Study design**

##### 37 **(A) Single-dose administration**

Cohort	Treatment	Sample size	Total Sample size	Food condition	Participants
A	Ensitrelvir 20 mg	1	8	Fasted	Japanese healthy adult male
	Placebo	1			
	Ensitrelvir 20 mg	5			
	Placebo	1			
B	Ensitrelvir 70 mg	6	8	Fasted	Japanese healthy adult male
	Placebo	2			
C <sup>a</sup>	Ensitrelvir 250 mg	4	5	Fasted in Period 1 and Fed <sup>b</sup> in Period 2	Japanese healthy adult male
	Placebo	1			
C <sup>a</sup>	Ensitrelvir 250 mg	4	5	Fed <sup>b</sup> in Period 1 and Fasted in Period 2	Japanese healthy adult male
	Placebo	1			
D	Ensitrelvir 500 mg	6	8	Fasted	Japanese healthy adult male
	Placebo	2			
E	Ensitrelvir 1000 mg	6	8	Fasted	Japanese healthy adult male

		Placebo	2	
	J1	Ensitrelvir 2000 mg	1	
J		Placebo	1	8
	J2	Ensitrelvir 2000 mg	5	
		Placebo	1	

38 <sup>a</sup>The effect of food was assessed in Cohort C; <sup>b</sup>High-fat/high-calorie meal, after breakfast.

39 **(B) Multiple-dose administration**

Cohort	Treatment		Group	Sample size	Total sample size	Participants
	Loading dose (Day 1)	Maintenance dose (Days 2-5/6)				
F	375 mg	125 mg	Ensitrelvir	8	11	Japanese healthy adult male
			Placebo	3		
G <sup>a</sup>	750 mg	250 mg	Ensitrelvir	8	11	
			Placebo	3		
H	375 mg	125 mg	Ensitrelvir	8	11	White healthy adult male
			Placebo	3		

40 <sup>a</sup>The effect of multiple-dose administration of ensitrelvir on the pharmacokinetics of midazolam (single dose 2mg [1 mL

41 syrup]) was investigated.