Supplementary Table 1 **Susceptibility to MCB of replicons containing NS5B coding region from clinical isolates**

Patient*	Study visit	GT	NS5B substitutions	Sample EC$_{50}$ MCB (μM) ± SD (n)	EC$_{50}$ fold /day 1	H77 ref EC$_{50}$ MCB (μM) ± SD (n)	EC$_{50}$ fold /H77
1*	Day 1	1A		0.25 ± 0.10 (4)		0.33 ± 0.13 (6)	0.76
	PDISC		S282T	0.81 ± 0.09 (3)	3.2	0.33 ± 0.13 (6)	2.4
	FUW8		none	0.26 ± 0.08 (8)	1.0	0.33 ± 0.13 (6)	0.79

Patient*	Study visit	GT	NS5B substitutions	Sample EC$_{50}$ MCB (μM, n=1)	EC$_{50}$ fold /day 1	Con1 ref EC$_{50}$ MCB (μM, n=1)	EC$_{50}$ fold /Con1
2	Day 1	1A		0.29		0.38	0.75
	PDISC		S282T	0.93	3.2	0.53	1.7
	FUW2		S282T	1.17	4.1	0.53	2.2
	FUW4		S282S/T	0.30	1.0	0.38	0.78
	FUW8		none	0.26	0.9	0.53	0.49
	FUW12		none	0.30	1.0	0.38	0.78
3	Day 1	1A		0.34		0.41	0.82
	W24		L159F/L +L320F**	0.55	1.6	0.41	1.3

*The NS5B coding region was cloned into H77 (GT 1a) replicon genetic background for patient 1, and Con1 (GT 1b) for patients 2 and 3. Patient 1 was tested in-house; patients 2 and 3 were tested at Monogram Sciences. The reference strain (ref) used for each assay is indicated.

**Initial sequencing showed L159F/L and L320F, repeated sequencing of samples used for phenotyping showed L320F only.

PDISC: premature discontinuation. FUW: follow-up week. W: week.

Supplementary Table 2   Susceptibility to DNV of replicons containing NS3 protease coding region from clinical isolates from patients who experienced viral breakthrough

Patient*	Study visit	GT	NS3 substitutions	Sample EC$_{50}$ DNV (nM) ± SD (n)	EC$_{50}$ fold /day 1	Con1 ref EC$_{50}$ DNV (nM) ± SD (n)	EC$_{50}$ fold /Con1
1	Day 1	1A		0.27 ± 0.06 (3)		0.15 ± 0.04 (9)	1.8
	Week 6		R155K	132 ± 21 (3)	492	0.15 ± 0.04 (9)	880
	PDISC		R155K	118 ± 23 (3)	442	0.15 ± 0.04 (9)	787
	FUW12		none	biphasic dose response curve (see Figure 2)			

Patient*	Study visit	GT	NS3 substitutions	Sample EC$_{50}$ DNV (nM, n=1)	EC$_{50}$ fold /day 1	Con1 ref EC$_{50}$ DNV (nM, n=1)	EC$_{50}$ fold /Con1
2	Day 1	1A		3.37		0.53	6.3
	PDISC		R155K	327	97	0.53	610
	FUW2		R155K	252	75	0.53	470
	FUW4		R155K	257	76	0.53	480
	FUW8		R155K	258	77	0.53	482
	FUW12		R155R/K	163	48	0.53	303
3	Day 1	1A		0.29		0.49	0.58
	W24		V36M, R155K	243	844	0.49	492
4	Day 1	1A		0.34		0.49	0.69
	W10		V36M, R155K	202	594	0.53	378
	FUW12		R155K	72	213	0.53	135
5	Day 1	1B		0.36		0.49	0.72
	W14		D168T	152	427	0.49	308
	FUW12		R155R/K/Q, D168D/A/N/T	56	158	0.49	114
6	Day 1	1B		0.27		0.49	0.54
	W18		V36G, D168E,	440	1645	0.49	889
	FUW4		R155K	106	397	0.49	215
	FUW12		R155R/K/Q, D168D/E	26	98	0.49	53

*The NS3 protease coding region was cloned into Con1 (GT 1b) replicon genetic background. Patient 1 was tested in-house; patients 2-6 were tested at Monogram Sciences. The reference strain (ref) used in the assay is indicated.

PDISC: premature discontinuation. FUW: follow-up week. W: week.

Supplementary Table 3   **Susceptibility to DNV of replicons containing NS3 protease coding region from clinical isolates from patients who relapsed**

Patient*	Study visit	GT	NS3 substitutions	Sample EC$_{50}$ DNV (nM, n=1)	EC$_{50}$ fold /Day 1	Con1 ref EC$_{50}$ DNV (nM, n=1)	EC$_{50}$ fold /Con1
7	Day 1	1B		0.30		0.49	0.61
	FUW4		D168E	43.6	145	0.49	88
8	Day 1	1B		0.15		0.49	0.30
	FUW8		R155R/Q, D168A	1.72	11.5	0.49	3.48
9	Day 1	1B		0.25		0.49	0.52
	Unscheduled		R155K	36.3	143	0.49	73
10	Day 1	1B		0.24		0.49	0.50
	FUW4		D168A	40.9	167	0.49	83
11	Day 1	1B		Not done	NA	NA	NA
	FUW2		V36A, D168E	254	NA	0.49	514
12	Day 1	1B	None	0.13		0.49	0.27
	FUW8		None	1.57	11.6	0.49	3.18
	FUW12		None	0.83	6.2	0.48	1.75
13	Day 1	1A		1.48		0.53	2.8
	FUW2		R155K	100	67.7	0.53	188
	FUW4		R155R/K, D168D/E	85.0	57.3	0.53	159
14	Day 1	1A		0.22		0.53	0.42
	FUW4		R155K	166	748	0.49	336
15	Day 1	1A		0.16		0.53	0.30
	FUW2		R155K	67.4	424	0.53	126
16	Day 1	1A		0.41		0.53	0.77
	FUW4		R155K	77.1	188	0.49	156
17	Day 1	1B	D168D/E	2.88		0.54	5.3
	FUW4		D168E	17.76	6.2	0.54	33
18	Day 1	1B		0.24		0.44	0.53
	FUW8		D168T	34.5	146	0.49	70

*The NS3 protease coding region was cloned into Con1 (GT 1b) replicon genetic background. All patients (7-18) were tested at Monogram Sciences. The reference strain (ref) used in the assay is indicated.
FUW: follow-up week. NA: not applicable.