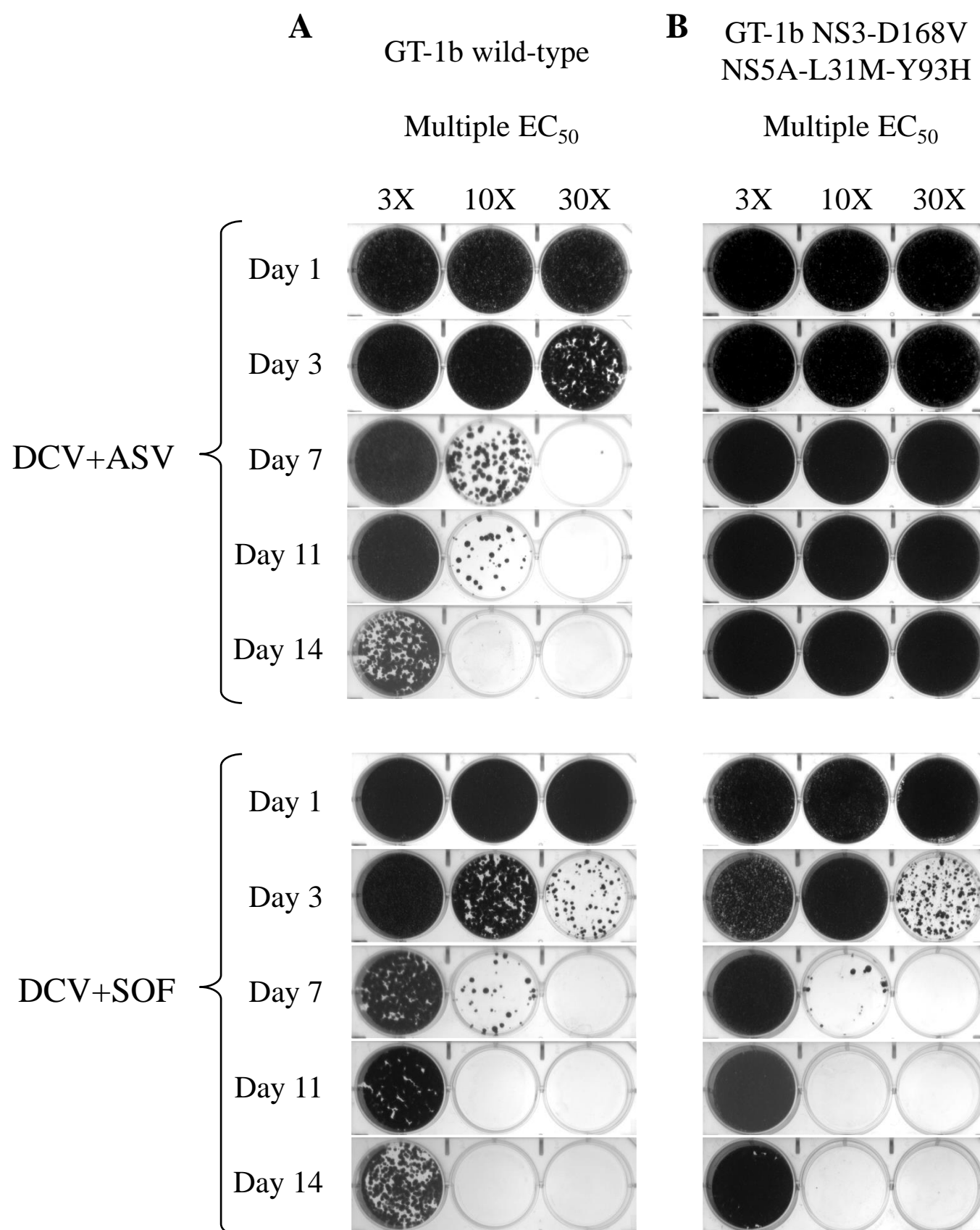


Supplementary Fig. 1 HCV replicon elimination assays with multiples of 50% effective concentration (EC_{50}) values for each agent ($3\times$, $10\times$, and $30\times EC_{50}$) determined in wild-type replicon. **(A)** wild-type GT-1b replicon cell lines and **(B)** daclatasvir+asunaprevir-resistant (NS3-D168V, NS5A-L31M-Y93H) replicon cell lines were incubated with the indicated regimen without G418 for 1, 3, 7, 11, and 14 days before the agents were removed and the cell cultures maintained for 2 weeks with G418 (0.5 mg/mL) to monitor replicon elimination. Due to concerns regarding cell toxicity, ribavirin was examined only at $1\times EC_{50}$ concentration. *Alfa* peginterferon alfa, *ASV* asunaprevir, *BCV* beclabuvir, *BMS-1* next-generation NS5A inhibitor, *BMS-2* next-generation NS3 protease inhibitor, *DCV* daclatasvir, *GT* genotype, *HCV* hepatitis C virus, *LDV* ledipasvir, *NS3* non-structural protein 3, *NS5A* non-structural protein 5A, *RBV* ribavirin, *SMV* simeprevir, *SOF* sofosbuvir



A

GT-1b wild-type

Multiple EC₅₀

3X 10X 30X

Day 1

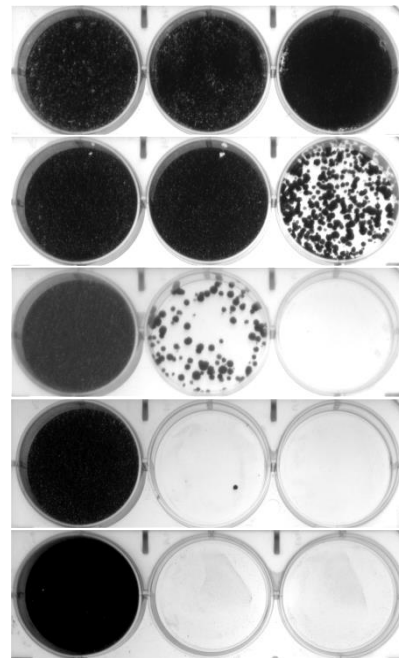
Day 3

Day 7

Day 11

Day 14

SOF+LDV

**B**

GT-1b NS3-D168V

NS5A-L31M-Y93H

Multiple EC₅₀

3X 10X 30X

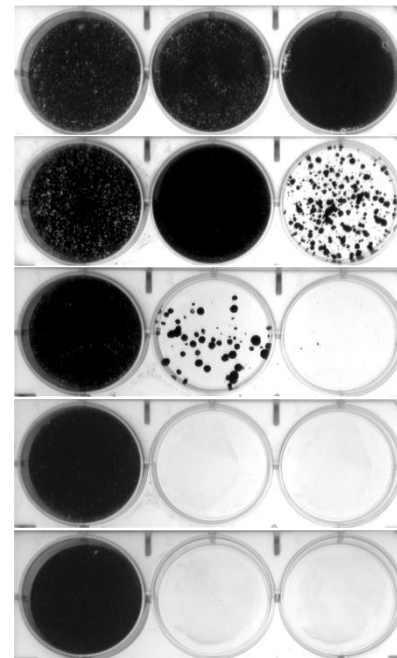
Day 1

Day 3

Day 7

Day 11

Day 14



Day 1

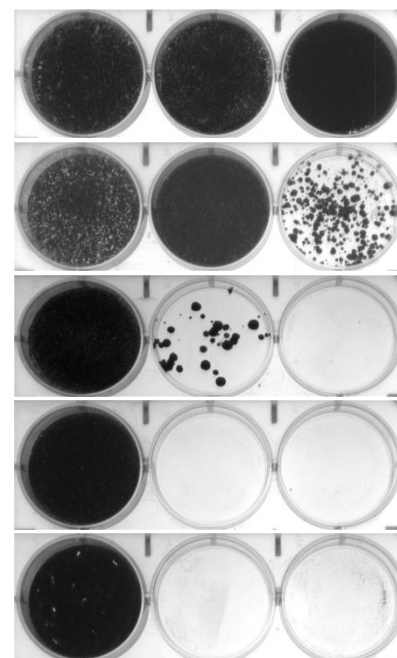
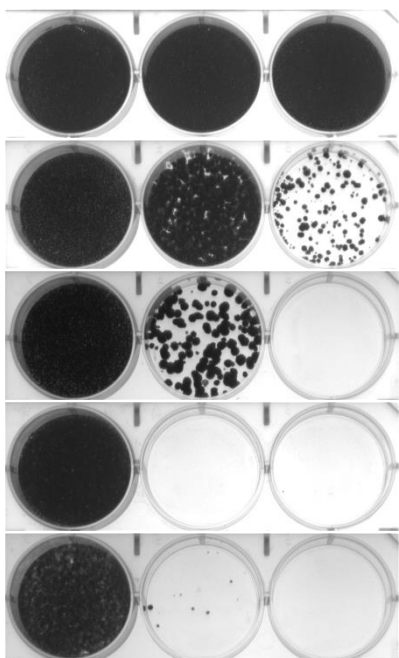
Day 3

Day 7

Day 11

Day 14

SOF+SMV



Day 1

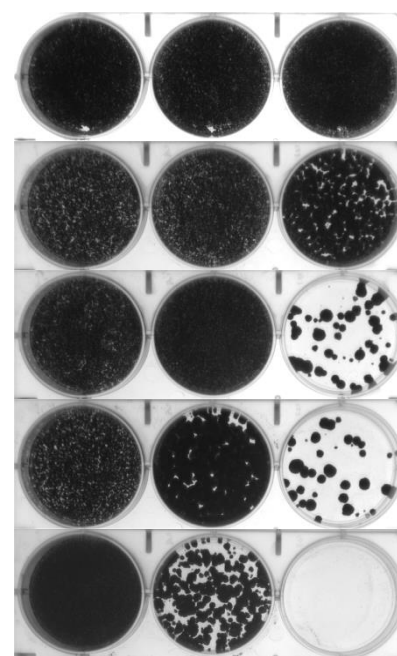
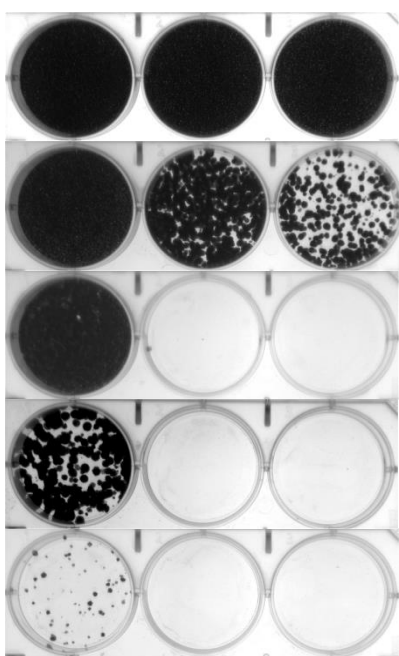
Day 3

Day 7

Day 11

Day 14

DCV+ASV+BCV



A

GT-1b wild-type

Multiple EC₅₀

3X 10X 30X

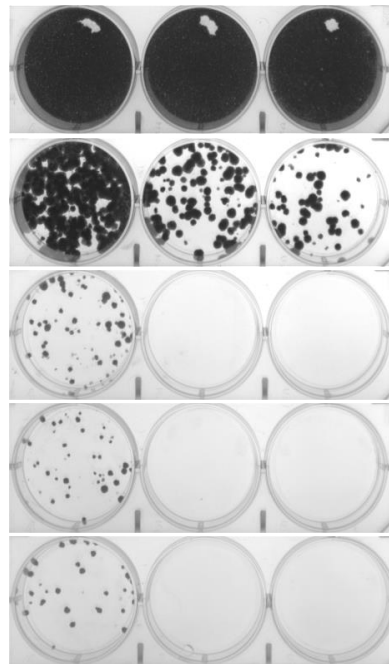
Day 1

Day 3

Day 7

Day 11

Day 14

DCV+ASV+
BCV+RBV**B**

GT-1b NS3-D168V

NS5A-L31M-Y93H

Multiple EC₅₀

3X 10X 30X

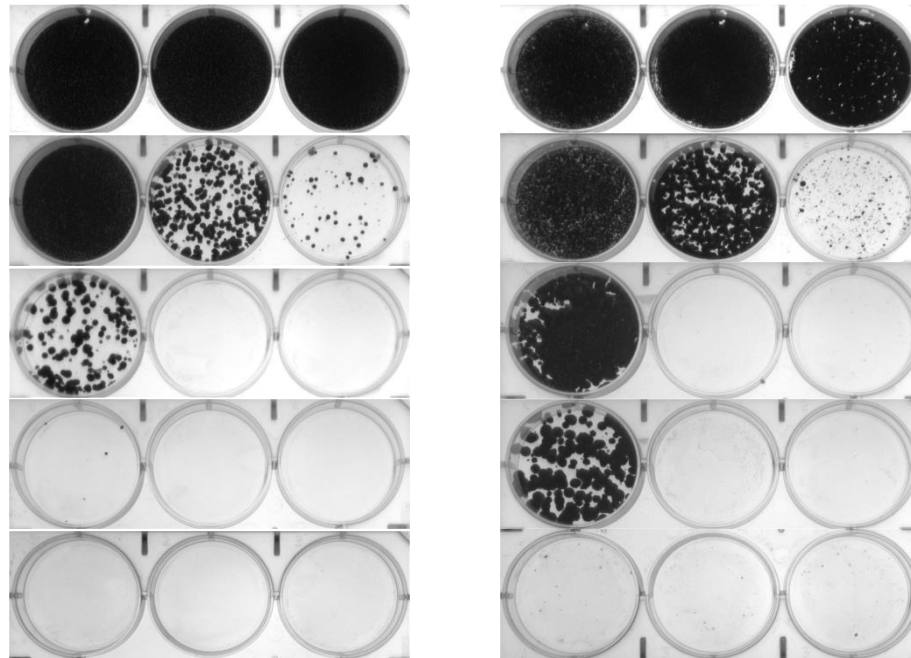
Day 1

Day 3

Day 7

Day 11

Day 14

DCV+ASV+
BCV+SOF

Day 1

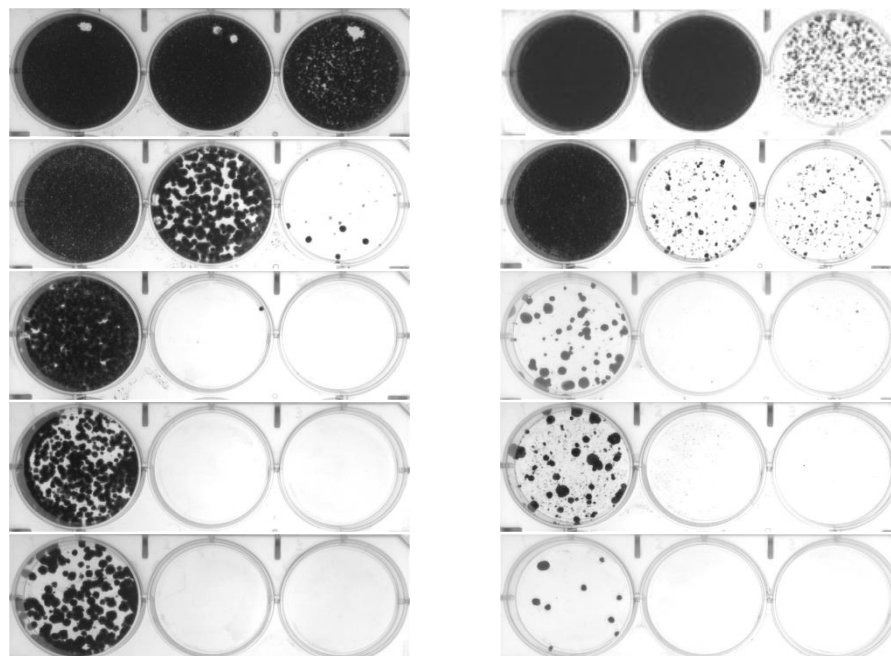
Day 3

Day 7

Day 11

Day 14

SOF+Alfa+RBV



A

GT-1b wild-type

Multiple EC₅₀

3X 10X 30X

Day 1

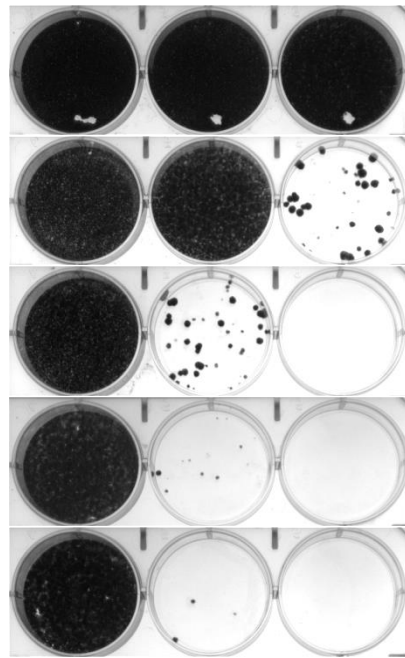
Day 3

Day 7

Day 11

Day 14

BCV+Alfa+RBV

**B**

GT-1b NS3-D168V

NS5A-L31M-Y93H

Multiple EC₅₀

3X 10X 30X

Day 1

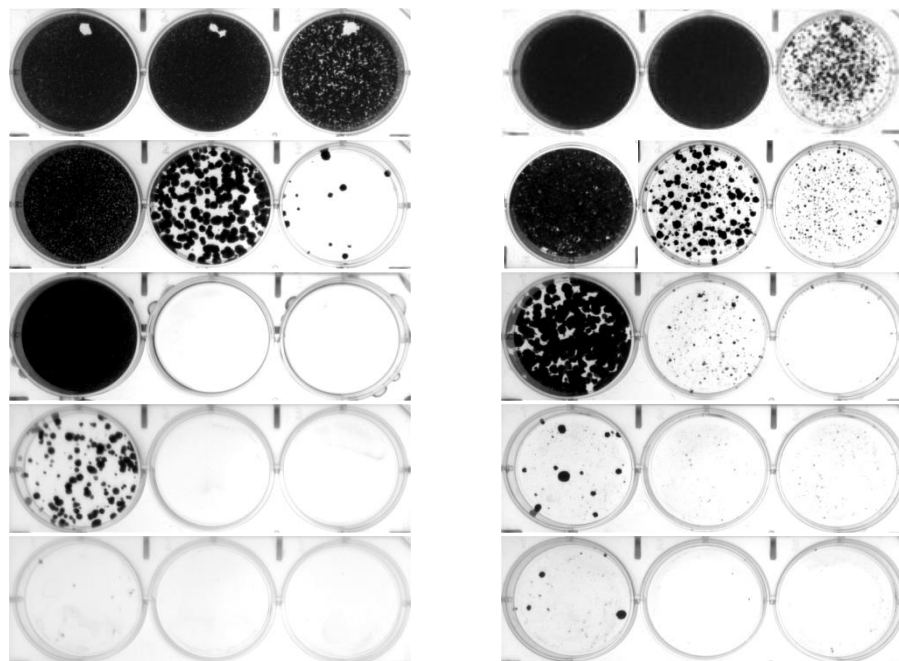
Day 3

Day 7

Day 11

Day 14

SOF+BMS-1



Day 1

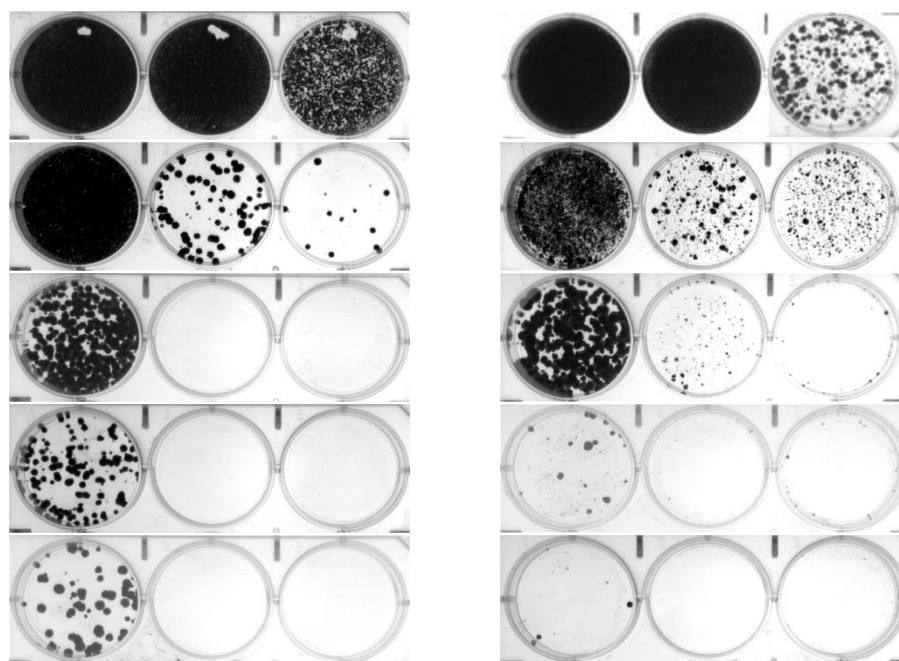
Day 3

Day 7

Day 11

Day 14

SOF+BMS-2



Supplementary Fig. 2 HCV replicon elimination assays with agent concentrations representing C_{trough} exposures observed in a clinical setting. Agents were incubated for 1, 2, 3, and 5 days with (A) wild-type GT-1b replicon cell lines, or (B) daclatasvir+asunaprevir-resistant (NS3-D168V NS5A-L31M-Y93H) replicon cell lines, before the agent was removed and the cell lines were incubated for 2 weeks to monitor replicon elimination. *Alfa* peginterferon alfa, *BCV* beclabuvir, *BMS-2* next-generation NS3 protease inhibitor, C_{trough} trough plasma concentrations, *HCV* hepatitis C virus, *LDV* ledipasvir, *NS3* non-structural protein 3, *NS5A* non-structural protein 5A, *RBV* ribavirin, *SOF* sofosbuvir

