Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53. DOI: 10.1056/NEJMoa1208809

The authors would like to express their gratitude to the investigators who made this study possible. ABT-450 was identified as a lead compound by Abbott and Enanta Pharmaceuticals.

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Virologic Stopping Rules:

Patients were required to stop study drug treatment if they met any of the following criteria: failure to achieve 2 $\log_{10}$ IU/mL HCV RNA decrease at week 1, confirmed HCV RNA increase from nadir >0.5 $\log_{10}$ IU/mL at any time, failure to achieve undetectable HCV RNA at week 6, or confirmed detectable HCV RNA at any point after undetectable HCV RNA. These criteria were selected to minimize ongoing viral replication in the presence of direct-acting antivirals, which could increase the risk for selection of resistant variants and compromise future treatment options. Failure to achieve a 2 $\log_{10}$ IU/mL reduction in the first week of dosing with an ABT-450/r-containing regimen would be strong evidence of inadequate viral suppression. Likewise, any confirmed increase in HCV RNA beyond that attributable to assay variability (approximately 0.5 $\log_{10}$ IU/mL), or any detectable HCV RNA after 6 weeks of study drug dosing, were considered presumptive evidence of ongoing viral replication in the presence of non-suppressive antiviral drug concentrations.

Figure S1A. Enrollment of Patients

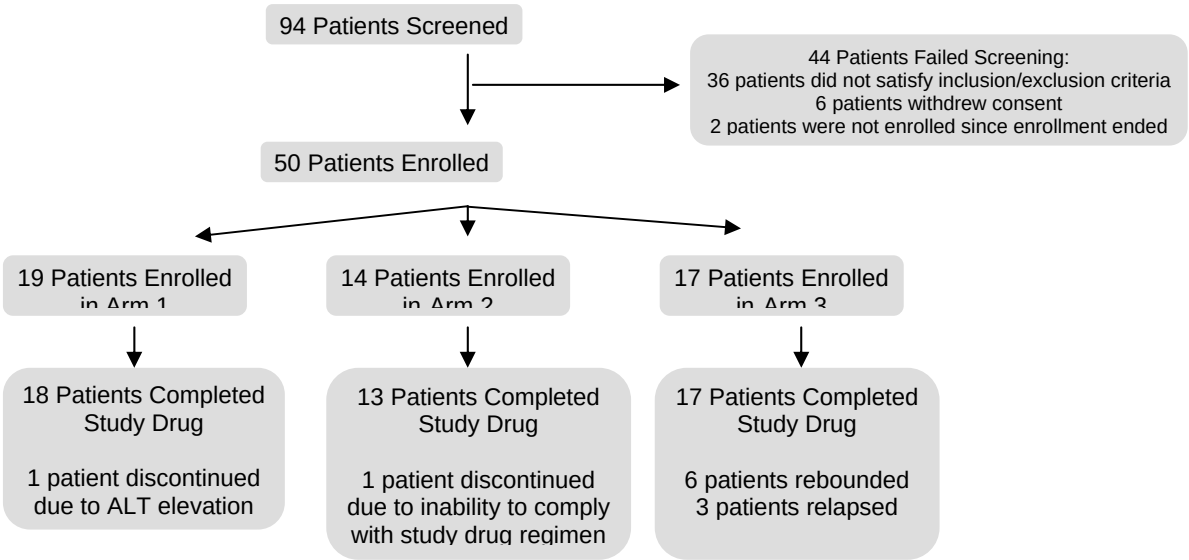

Figure S1B. Individual HCV RNA Values through 12 Weeks of Treatment and 36 Weeks of Post-Treatment Follow-up in Arm 1

IL28B	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CT	CT	CT	CT	CT	CT	CT	TT	TT
Genotyp	1a	1a	1a	1a	1a	1a	1a	1a	1a	1a	1b	1a	1a	1b	1a	1a	1a	1a	1a
BL	$5.5x10^6$	$2.5x10^6$	$8.3x10^5$	$1.0x10^7$	$1.3x10^7$	$7.6x10^6$	$5.2x10^6$	$2.1x10^5$	$1.2x10^5$	$1.4x10^4$	$3.3x10^6$	$1.0x10^7$	$1.5x10^7$	$6.5x10^5$	$3.1x10^5$	$2.3x10^6$	$2.7x10^6$	$6.3x10^6$	$1.0x10^6$
Wk 1	162	133	49	108	154	100	88	<25	<25	U	146	84	549	<25	<25	<25	35	159	<25
Wk 2	<25	<25	<25	58	<25	<25	<25	U	U	U	U	<25	<25	U	U	<25	U	<25	U
Wk 3	<25	<25		<25	<25	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 4	<25	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 5	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 6	<25	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 7	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 8	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 9	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 10	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 11	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Wk 12	U	U		U		U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW 2	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW 4	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW 8	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW12	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW24	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW36	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
PTW48	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U

U=Undetectable (HCV RNA not detected), <25 = <25 IU/mL (HCV RNA detected)
1 subject discontinued due to ALT elevation

Figure S1C. Individual HCV RNA Values through 12 Weeks of Treatment and 24 Weeks of Post-Treatment Follow-up in Arm 2

IL28B	CC	CC	CC	CC	CC	CT	CT	CT	CT	CT	CT	CT	TT	TT
Genotype	1a	1a	1a	1b	1a	1a	1a	1a	1a	1a	1a	1b	1b	1a
Baseline	$2.3x10^5$	$3.0x10^7$	$1.3x10^3$	$1.1x10^7$	$7.8x10^6$	$2.1x10^5$	$3.5x10^6$	$1.3x10^7$	$1.0x10^7$	$5.2x10^6$	$1.4x10^7$	$3.6x10^6$	$6.7x10^6$	$1.2x10^7$
Wk 1	<25		U	88	270	<25	26	89	72	<25	181	49	297	27
Wk 2	U		U	U	<25	U	<25	<25	<25	U	<25	<25	52	U
Wk 3	U		U	U	U	U	U	<25	<25	U	U	U	30	U
Wk 4	U		U	U	U	U	U	<25	U	U	U	U	<25	U
Wk 5	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 6	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 7	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 8	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 9	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 10	U		U	U	U	U	U	U	U	U	U	U	U	U
Wk 11	U		U	U	U	U	U	U	U	U	U	U	26	U
Wk 12	U		U	U	U	U	U	U	U	U	U	U	U	U
PTW 2	U		U	U	U	U	U	U	U	U	U	U	U	U
PTW 4	U		U	U	U	U	U	U	U	U	U	U	U	U
PTW 8	U		U	U	U	U	U	U	U	U	U	U	U	U
PTW12	U		U	U	U	U	U	U	U	U	U	U	U	U
PTW24	U		U		U	U	U	U	U	U	U	U	U	U
PTW36	U		U		U	U	U	U	U		U	U	U	U
PTW48	U		U		U	U	U	U	U		U	U	U	U

U=Undetectable (HCV RNA not detected), <25 = <25 IU/mL (HCV RNA detected)
1 subject discontinued due to noncompliance caused by personal issues

Figure S1D. Individual HCV RNA Values through 12 Weeks of Treatment and 12 Weeks of Post-Treatment Follow-up in Arm 3

IL28B	CT	CT	CT	CT	CT	CT	CT*	CT	CT	CT	CT	CT	TT	TT	TT	TT	TT
Genotype	1a	1a	1a	1a	1a	1a	1a	1b	1a	1a	1a	1a	1a	1a	1a	1a	1a
Baseline	$2.6x10^7$	$5.6x10^7$	$1.7x10^7$	$2.4x10^6$	$1.0x10^6$	$1.1x10^6$	$1.6x10^7$	$3.2x10^7$	$8.8x10^6$	$1.7x10^7$	$4.2x10^6$	$8.5x10^6$	$5.4x10^6$	$1.4x10^7$	$2.4x10^6$	$1.2x10^7$	$2.2x10^6$
Wk 1	32	42	172	<25	U	<25	222	538	U	236	44	170	181	48	108	192	87
Wk 2	U	U	<25	U	U	U	63	31	U	37	U	<25	<25	<25	<25	<25	<25
Wk 3	U	249	U	U	U	U	570	<25	U	U	U	U	<25	<25	U	U	<25
Wk 4	U	45300	U	U	U	U	19800	<25	U	U	U	U	<25	U	U	U	U
Wk 5	U		U	U	U	U	54600	520	U	U	U	U	1990	U	U	U	U
Wk 6	U		U	U	U	U		20200	U	U	U	27	54500	U	U	U	U
Wk 7	U		U	U	U	U			U	U	U	U		U	U	U	U
Wk 8	U		U	U	U	U			U	U	U	U		U	U	U	<25
Wk 9	U		U	U	U	U			U	U	U	U		U	U	U	61
Wk 10	U		U	U	U	U			U	U	U	U		U	U	U	4240
Wk 11	U		U	U	U	U			U	U	U	U		U	<25	U	
Wk 12	U		<25	U	U	U			U	U	U	U		U	861	U	
PTW 2	2000		176	U	U	30			U	U	U	U		U		U	
PTW 4	1160000			U	U	2400000			U	U	U	U		U		U	
PTW 8				U	U				U	U	U	U		U		U	
PTW12				U	U				U	U	U	U		U		U	
PTW24				U	U				U	U	U	U		U		U	
PTW36				U	U				U	U	U	U		U		U	

*Underdosed for first 3 weeks

U=Undetectable (HCV RNA not detected), <25 = <25 IU/mL (HCV RNA detected)

Table S1. Treatment-Emergent Adverse Events (All)

	Arm 1 **Treatment-naïve** **ABT-450/r 250/100 mg** **QD +** **ABT-333 400 mg BID +** **RBV** **N=19**	**Arm 2** **Treatment-naïve** **ABT-450/r 150/100 mg** **QD +** **ABT-333 400 mg BID +** **RBV** **N=14**	**Arm 3** **Non-responders** **ABT-450/r 150/100 mg** **QD +** **ABT-333 400 mg BID +** **RBV** **N=17**
Adverse Events			
Fatigue, n (%)	9 (47.4)	6 (42.9)	6 (35.3)
Nausea	4 (21.1)	3 (21.4)	4 (23.5)
Headache	5 (26.3)	2 (14.3)	3 (17.6)
Dizziness	1 (5.3)	4 (28.6)	4 (23.5)
Insomnia	5 (26.3)	3 (21.4)	0
Pruritus	4 (21.1)	0	2 (11.8)
Rash	4 (21.1)	1 (7.1)	1 (5.9)
Vomiting	1 (5.3)	3 (21.4)	0
Anemia	2 (10.5)	1 (7.1)	1 (5.9)
Leukocytosis	0	1 (7.1)	0
Lymphadenopathy	0	1 (7.1)	0
Tachycardia	0	1 (7.1)	0
Ear Pain	0	0	1 (5.9)
Eye Haemorrhage	0	0	1 (5.9)
Lacrimation Increased	1 (5.3)	0	0
Photophobia	0	1 (7.1)	0
Abdominal Discomfort	1 (5.3)	0	1 (5.9)
Abdominal Distension	0	1 (7.1)	0
Cheilitis	0	0	1 (5.9)
Constipation	2 (10.5)	0	0
Dental Caries	0	1 (7.1)	0
Diarrhea	2 (10.5)	1 (7.1)	2 (11.8)
Dyspepsia	0	1 (7.1)	0
Epigastric Discomfort	0	0	1 (5.9)

Flatulence	0	1 (7.1)	1 (5.9)
Frequent Bowel Movements	1 (5.3)	0	0
Gastritis	1 (5.3)	0	0
Gastroesophageal Reflux Disease	2 (10.5)	0	0
Asthenia	1 (5.3)	0	0
Chest Pain	0	1 (7.1)	0
Chills	0	0	1 (5.9)
Energy Increased	0	1 (7.1)	0
Feeling Abnormal	1 (5.3)	0	0
Hunger	0	0	1 (5.9)
Influenza Like Illness	0	1 (7.1)	0
Injection Site Reaction	0	0	1 (5.9)
Irritability	1 (5.3)	2 (14.3)	1 (5.9)
Non-Cardiac Chest Pain	1 (5.3)	0	0
Oedema Peripheral	3 (15.8)	1 (7.1)	0
Pain	2 (10.5)	0	0
Pyrexia	0	0	1 (5.9)
Hyperbilirubinaemia	1 (5.3)	0	0
Seasonal Allergy	1 (5.3)	0	0
Body Tinea	1 (5.3)	0	0
Bronchitis	1 (5.3)	0	0
Cellulitis	1 (5.3)	0	0
Folliculitis	0	1 (7.1)	0
Gastroenteritis	0	0	1 (5.9)
Hordeolum	0	0	1 (5.9)
Influenza	0	0	1 (5.9)
Pneumonia	0	0	1 (5.9)
Sinusitis	0	1 (7.1)	0
Tinea Pedis	0	1 (7.1)	0
Upper Respiratory Tract Infection	2 (10.5)	0	1 (5.9)
Urinary Tract Infection	1 (5.3)	0	0
Viral Upper Respiratory	0	1 (7.1)	0

Tract Infection			
Laceration	0	1 (7.1)	0
Muscle Strain	0	1 (7.1)	0
Procedural Pain	0	1 (7.1)	0
Sunburn	0	1 (7.1)	0
Alanine Aminotransferase Increased	1 (5.3)	0	1 (5.9)
Aspartate Aminotransferase Increased	1 (5.3)	0	0
Blood Creatinine Increased	1 (5.3)	0	0
Blood Oestrogen Increased	0	0	1 (5.9)
Creatinine Renal Clearance Decreased	1 (5.3)	0	0
Electrocardiogram QT Prolonged	1 (5.3)	0	0
Heart Rate Increased	0	1 (7.1)	1 (5.9)
Decreased Appetite	2 (10.5)	2 (14.3)	0
Diabetes Mellitus	0	0	1 (5.9)
Hyperglycaemia	1 (5.3)	0	0
Hypokalaemia	0	0	1 (5.9)
Arthralgia	1 (5.3)	2 (14.3)	0
Back Pain	2 (10.5)	1 (7.1)	1 (5.9)
Flank Pain	2 (10.5)	0	0
Muscle Spasms	1 (5.3)	0	1 (5.9)
Myalgia	0	1 (7.1)	1 (5.9)
Pain in Extremity	0	1 (7.1)	0
Cognitive Disorder	0	1 (7.1)	0
Coordination Abnormal	0	0	1 (5.9)
Dysgeusia	1 (5.3)	1 (7.1)	1 (5.9)
Hypoaesthesia	1 (5.3)	0	0
Lethargy	0	0	1 (5.9)

Memory Impairment	1 (5.3)	0	0
Migraine	0	0	1 (5.9)
Paraesthesia	2 (10.5)	2 (14.3)	0
Poor Quality Sleep	0	2 (14.3)	0
Sinus Headache	0	0	1 (5.9)
Tremor	1 (5.3)	0	0
Abnormal Dreams	0	1 (7.1)	0
Affect Lability	1 (5.3)	0	0
Agitation	1 (5.3)	1 (7.1)	0
Anxiety	0	0	1 (5.9)
Confusional State	0	0	1 (5.9)
Depressed Mood	0	1 (7.1)	0
Depression	2 (10.5)	0	0
Disorientation	0	1 (7.1)	0
Hypervigilance	0	1 (7.1)	0
Libido Decreased	1 (5.3)	0	0
Nervousness	0	0	1 (5.9)
Sleep Disorder	0	1 (7.1)	0
Dysuria	2 (10.5)	1 (7.1)	0
Micturition Urgency	1 (5.3)	0	0
Pollakiuria	1 (5.3)	0	0
Renal Failure Acute	1 (5.3)	0	0
Dyspareunia	0	0	1 (5.9)
Vulvovaginal Dryness	1 (5.3)	0	0
Cough	1 (5.3)	0	0
Dyspnoea	2 (10.5)	0	1 (5.9)
Dyspnoea Exertional	1 (5.3)	0	1 (5.9)
Haemoptysis	1 (5.3)	0	0
Nasal Congestion	1 (5.3)	0	0
Oropharyngeal Pain	0	1 (7.1)	0
Paranasal Sinus Hypersecretion	1 (5.3)	0	0
Productive Cough	1 (5.3)	0	0
Respiratory Tract Congestion	1 (5.3)	0	1 (5.9)

Sinus Congestion	0	0	1 (5.9)
Alopecia	0	0	1 (5.9)
Cold Sweat	0	1 (7.1)	0
Dermatitis Contact	0	1 (7.1)	0
Dry Skin	1 (5.3)	0	0
Dyshidrosis	1 (5.3)	0	0
Puritus Generalized	3 (15.8)	1 (7.1)	0
Skin Odor Abnormal	1 (5.3)	1 (7.1)	0
Urticaria	1 (5.3)	0	0
Flushing	1 (5.3)	0	0
Hot Flush	1 (5.3)	1 (7.1)	0
Hypertension	0	0	1 (5.9)