ONLINE EXPERT POSTER REVIEW AND DISCUSSION

REPORTING FROM

The 47th Annual Meeting of the European Association for the Study of the Liver (EASL)

JOINTLY SPONSORED BY THE POSTGRADUATE INSTITUTE FOR MEDICINE AND VIRALED, LLC.

A 12-Week Interferon-Free Regimen of ABT-450/r, ABT-072, and Ribavirin was Well Tolerated and Achieved Sustained Virologic Response in 91% Treatment-Naïve HCV IL28B-CC Genotype-1-Infected Subjects

Eric Lawitz, Fred Poordad, Kris V. Kowdley, Donald Jensen, Daniel E. Cohen, Sara Siggelkow, Karen Wikstrom, Lois Larsen, Rajeev M. Menon, Thomas Podsadecki, Barry Bernstein

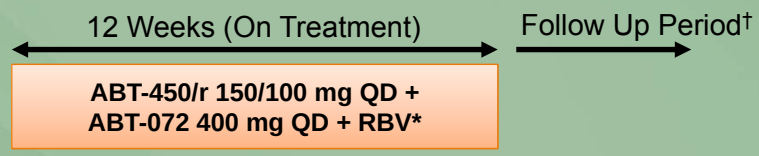
Abstract #13

Background

- There are presently no treatment options for HCV genotype 1 (GT1)-infected patients who are unable to take interferon-based therapy
- ABT-450, identified as a lead compound by Abbott and Enanta, is a potent inhibitor of the HCV NS3 protease that is metabolized by cytochrome P450 isoform 3A (CYP3A)
- ABT-450 is co-administered with ritonavir (ABT-450/r), a CYP3A inhibitor, to maintain high ABT-450 exposures and support once-daily (QD) dosing
- ABT-072 is a non-nucleoside inhibitor of HCV NS5B polymerase and is dosed QD
- This pilot study is the first interferon-free evaluation of ABT-450/r + ABT-072 + RBV in GT1-infected subjects
- Enrollment was limited to patients with the IL28B SNP rs12979860 CC genotype to maximize chances of successful rescue with peginterferon + RBV in the event of treatment failure of the study regimen[1,2]

1. *Nature*. 2009;461(7262):399-401. 2. *Gastroenterology*. 2010;139(1):120-129 e118.

M12-267 Study Design



- Efficacy Analyses:
  - Primary endpoint
    - Percentage of subjects achieving extended rapid virologic response (eRVR, HCV RNA <LLOQ from week 4 through week 12 of treatment)
  - Secondary endpoints
    - Percentage of subjects achieving HCV RNA <LLOQ at week 4 (RVR)
    - Percentage of subjects achieving HCV RNA <LLOQ 12 weeks post-treatment (SVR12) and 24 weeks post-treatment (SVR24)

†All subjects followed for 48 weeks after end of treatment
*Weight-based ribavirin 1000-1200mg/day

Registered with ClinicalTrials.gov as NCT01221298

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Demographics and Baseline Disease Characteristics

	N=11
Male, n (%)	8 (72.7)
White, n (%)	9 (81.8)
Hispanic/Latino, n (%)	3 (27.3)
Mean Age ± SD (years)	56.4 ± 7.35
Mean Weight ± SD (kg)	79.6 ± 10.60
Mean BMI ± SD (kg/m^2)	26.9 ± 3.17
IL28 Genotype CC, n (%)	11 (100)
HCV Genotype, n (%) 1a 1b	 8 (72.7) 3 (27.3)
Mean HCV RNA ± SD ($\log_{10}$ IU/mL)	6.93 ± 0.22
HCV RNA >800,000 IU/mL, n (%)	11 (100)

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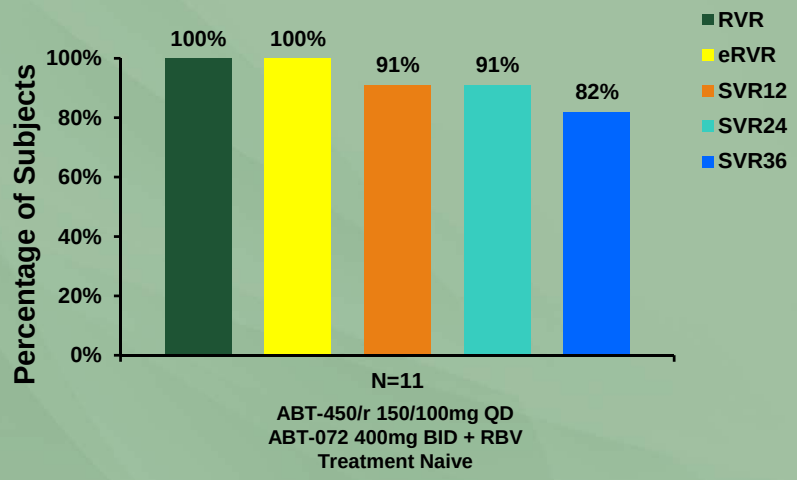
Virologic Results Based on Assay Lower Limit of Quantitation (LLOQ)



eRVR: pre-specified primary analysis based on HCV RNA < LLOQ

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Resistance Analysis

Genotype	1a	1b	1a	1a	1b	1a	1a	1b	1a	1a	1a
BL	1.1 X 10^7	1.3 X 10^7	4.0 X 10^6	5.8 X 10^6	1.2 X 10^7	3.4 X 10^6	1.2 X 10^7	9.2 X 10^6	7.7 X 10^6	1.9 X 10^7	9.1 X 10^6
Wk 1	86	333	<25	160	82	<25	190	112	426	66	<25
Wk 2	<25	38	U	<25					<25	U	U
Wk 3	U	<25	U	<25					<25	U	U
Wk 4	U	U	U	U					U	<25	U
Wk 5	U	U	U	U					U	U	U
Wk 6	U	U	U	U					U	U	U
Wk 7	U	U	U	U	U	U	U	U	U	U	U
Wk 8	U	U	U	U	U						U
Wk 9											U
Wk 10											U
Wk 11											U
Wk 12											U
PTW 2											U
PTW 4											U
PTW 8						U	U	U	U	765	U
PTW12						U	U	U	U	7840000	U
PTW16	U	U	U	U	U	U	U	U	U		U
PTW24	U	U	U	U	U	U	U	U	U		U
PTW36	U	U	4580000	U	U	U	U	U	U		U

Wild type at all signature resistance amino acid positions in NS3 protease and NS5B polymerase

Protease: 99% of clones were wild type at signature resistance amino acid positions
Polymerase: Y448H in 99% of clones

Protease: D168V in 36% of clones
Polymerase: 99% of clones were wild type at signature resistance amino acid positions

U: HCV RNA not detected; <25: <25 IU/mL (HCV RNA detected)

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Treatment-Emergent Potentially Clinically Significant Laboratory Abnormalities

	N=11
Total Bilirubin ≥ 2X ULN	2 (18.2)
Fasting Glucose > 250 mg/dL (13.8 mmol/L)	1 (9.1)

- Bilirubin elevations consisted of indirect bilirubin with no associated transaminase elevations
- Maximum bilirubin elevations were 2.8 and 2.7 mg/dL (48 and 46 µmol/L)
- Both bilirubin elevations occurred 1 week after starting treatment and resolved with continued dosing
  - Consistent with the known effect of ABT-450 on the bilirubin transporter OATP1B1

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Summary

- 91% of treatment-naïve, non-cirrhotic HCV GT1-infected subjects with IL28B CC genotype achieved SVR_{12} and 82% achieved SVR_{36}
- The combination of ABT-450/r + ABT-072 + RBV is well tolerated during 12 weeks of treatment
- There were no breakthroughs on therapy and two relapses post-therapy
  - No additional relapses seen among 10 subjects with 48-week post-treatment data available

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A 12-Week Interferon-Free Regimen of ABT-450/r + ABT-333 + Ribavirin Achieved SVR_{12} in More Than 90% of Treatment-Naïve HCV Genotype-1-Infected Subjects and 47% of Previous Non-Responders

Fred Poordad, Eric Lawitz, Kris V. Kowdley, Gregory T. Everson, Bradley Freilich, Daniel Cohen, Sara Siggelkow, Michele Heckaman, Rajeev Menon, Tami Pilot-Matias, Thomas Podsadecki, Barry Bernstein

Abstract #1399

Co-Pilot (M12-746) Study Design

	12 Weeks (On Treatment)	Follow Up Period†
Arm 1 Treatment-naïve (N=19)	ABT-450/r 250/100 mg QD + ABT-333 400 mg BID + RBV*	
Arm 2 Treatment-naïve (N=14)	ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV*	
Arm 3 Prior P/R non-responders (N=17)	ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV*	

†All subjects followed for 48 weeks after end of treatment
*Weight-based ribavirin 1000-1200mg/day

Registered with ClinicalTrials.gov as NCT01306617
Poordad F et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

Key Eligibility Criteria

- Chronic HCV genotype 1 infection
- Liver biopsy within the past 3 years consistent with chronic HCV and no evidence of extensive bridging fibrosis or cirrhosis
- Treatment-naïve: Subject never received previous HCV treatment
- Previous non-responders to P/R per protocol defined as:
  - Failed to achieve 2 log10 HCV RNA decrease by week 12 (null responder), or
  - Failed to achieve HCV RNA below the limit of detection during treatment (partial responder)
- Absence of HIV or hepatitis B co-infection

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Study Aims

- Efficacy Analyses
  - Primary Endpoint
    - Extended rapid virologic response (eRVR, HCV RNA <LLOD from treatment weeks 4 through 12)
  - Secondary Endpoints
    - HCV RNA <LLOQ 4 weeks post-treatment (SVR4)
    - HCV RNA <LLOQ 12 weeks post-treatment (SVR12)

HCV RNA measured using Roche COBAS TaqMan® v2.0 assay (lower limit of quantitation [LLOQ] = 25 IU/mL, lower limit of detection [LLOD] = 15 IU/mL)

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Demographics and Baseline Characteristics

	Arm 1 Treatment-naïve ABT-450/r 250/100 mg + ABT-333 400 mg + RBV N=19	Arm 2 Treatment-naïve ABT-450/r 150/100 mg +ABT-333 400 mg+ RBV N=14	Arm 3 Non-responders ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=17
Male, n (%)	10 (52.6)	14 (100)	11 (64.7)
White, n (%)	15 (78.9)	12 (85.7)	13 (76.5)
Hispanic/Latino, n (%)	3 (15.8)	0	4 (23.5)
Mean Age ± SD (years)	53.6 ± 9.78	50.9 ± 10.45	52.3 ± 9.03
Mean BMI ± SD (kg/m^2)	27.3 ± 3.84	24.6 ± 3.08	27.6 ± 4.65
IL28 genotype , n (%)			
CC	10 (52.6)	5 (35.7)	0
CT	7 (36.8)	7 (50.0)	12 (70.6)
TT	2 (10.5)	2 (14.3)	5 (26.3)
HCV genotype, n (%)			
1a	17 (89.5)	11 (78.6)	16 (94.1)
1b	2 (10.5)	3 (21.4)	1 (5.9)
HCV RNA			
Mean ± SD ($\log_{10}$ IU/mL)	6.25 ± 0.80	6.44 ± 1.15	6.93 ± 0.47
>800,000 IU/mL, n (%)	14 (73.7)	11 (78.6)	17 (100)
Non-responder status			
Partial responder	-	-	11 (64.7)
Null responder			6 (35.3)

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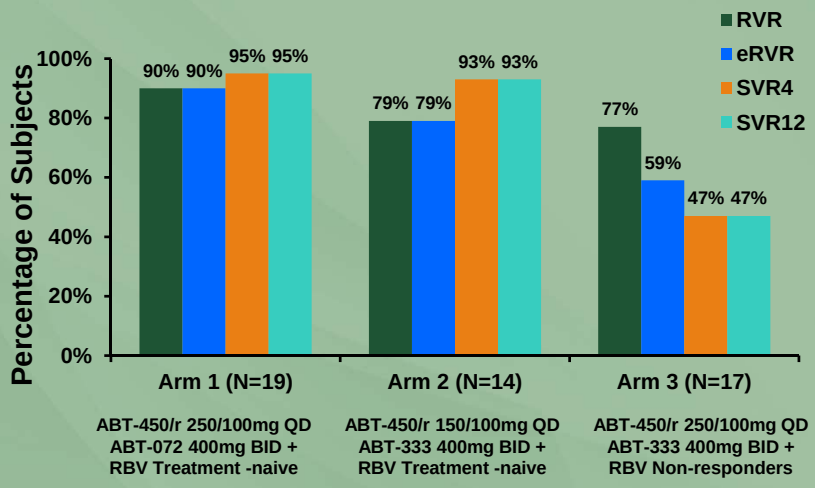
Virologic Results by Treatment Arm based on Assay Limit of Detection (LLOD)



eRVR: pre-specified primary analysis based on HCV RNA < LLOD

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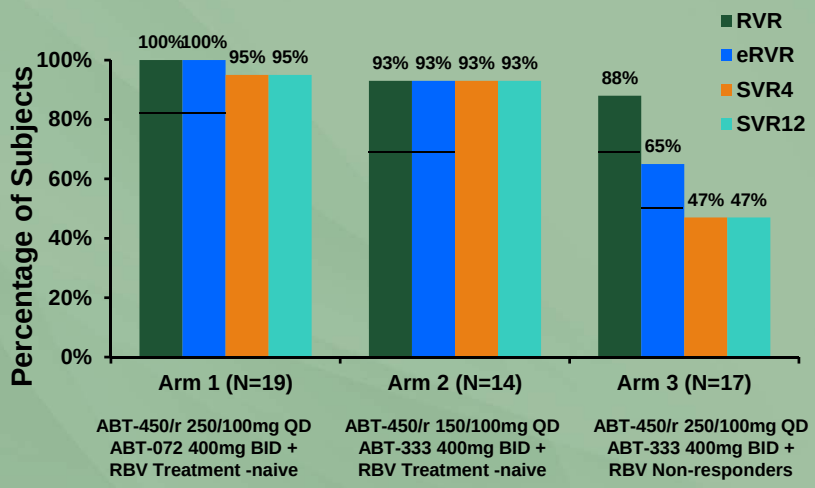
Virologic Results by Treatment Arm based on Assay Limit of Quantitation (LLOQ)



eRVR: pre-specified primary analysis based on HCV RNA < LLOD

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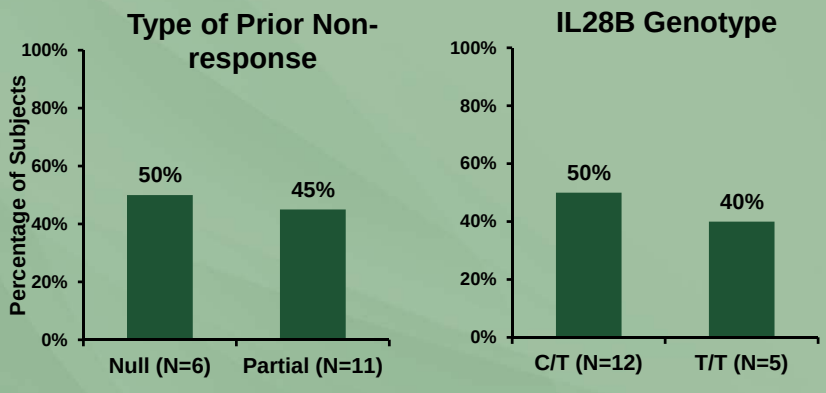
SVR_{12} in Subgroups of Arm 3 (Prior Non-Responders)



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Resistant Variants Present at Baseline and at Time of Virologic Failure in Previous Non-Responders

	GT	NS3 protease		NS5B polymerase	
		Baseline	At time of failure	Baseline	At time of failure
On-treatment failure	1a	None	R155K > D168A > D168V	None	G554S
	1a	None	D168A	None	M414T
	1a	None	D168V	None	C316Y > D559G
	1a	None	D168E > D168Y	None	G554S > S556G
	1a	None	D168V	None	S556G
	1b	D168E, D168T*	D168K	None	C316Y
Post-treatment relapse	1a	None	D168Y > D168V > D168A	None	M414T+S556G
	1a	None	None	None	None
	1a	None	D168V	None	S556G

Results based on clonal sequencing of ≥ 80 clones per sample
None = no variants at amino acid positions where resistance is known to occur
* D168E or D168T to D168K in GT 1b requires only a single nucleotide change

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Discontinuations, Dose Reductions, and Severe Adverse Events

- No deaths or serious adverse events
- One adverse event leading to premature discontinuation in Arm 1
  - Isolated ALT and AST elevation at week 2 (maximum ALT = 308 U/L, Grade 3)
  - Asymptomatic, no associated bilirubin increase
  - ALT and AST improved promptly after study drug discontinuation
- Four subjects with adverse events assessed as severe, none requiring study drug interruption or discontinuation
  - Hyperbilirubinemia (maximum 6.2 mg/dL [106 mmol/L]), predominantly indirect bilirubin, led to ribavirin dose reduction
  - Fatigue
  - Pain
  - Vomiting

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Treatment-Emergent Adverse Events (>20% in any Arm)

	Arm 1 Treatment-naïve ABT-450/r 250/100 mg + ABT-333 400 mg + RBV N=19	Arm 2 Treatment-naïve ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=14	Arm 3 Non-responders ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=17
Fatigue	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

*All rash events were mild and most resolved during study drug treatment

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Laboratory Abnormalities of Note

	Arm 1 Treatment-naïve ABT-450/r 250/100 mg + ABT-333 400 mg + RBV N=19	Arm 2 Treatment-naïve ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=14	Arm 3 Non-responders ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=17
Total bilirubin ≥ 2X ULN, n (%)	3 (15.8)	3 (21.4)	0
Creatinine ≥ 1.5 mg/dL*	2 (10.5)	0	0
Calculated creatinine clearance < 50 mL/min*	2 (10.5)	0	0
ALT ≥ 5X ULN	1 (5.3)	0	0
Sodium < 130 mmol/L	0	1 (7.1)	0

- Bilirubin elevations consisted of indirect bilirubin and were consistent with the known effect of ABT-450 on the bilirubin transporter OATP1B1
- Maximum bilirubin elevation was 6.4 mg/dL

* Creatinine elevations and creatinine clearance elevations occurred in the same subjects

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Laboratory Abnormalities of Note (continued)

- All bilirubin elevations consisted of indirect bilirubin
  - 3/6 subjects had elevations > 2x ULN at a single visit only
  - All resolved without DAA dose adjustment while on treatment
  - Consistent with the known effect of ABT-450 on the bilirubin transporter OATP1B1
- Of the subjects with creatinine values ≥ 1.5 mg/dL
  - 1 subject had a value of 1.7 mg/dL at a single visit
  - 1 subject had a value of 1.7 mg/dL at a single visit and a value of 2.5 mg/dL at a second non-consecutive visit
  - Both resolved without DAA dose adjustment while on treatment

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Conclusions: Efficacy

- 93-95% of treatment-naïve subjects infected with HCV genotype 1 achieved SVR12 after 12 weeks of treatment
  - No virologic failures occurred among treatment-naïve subjects who completed study drug treatment
- ABT-450/r 250/100 mg and 150/100 mg doses showed comparable response rates in treatment-naïve subjects
- 47% of previous non-responders achieved SVR12 after 12 weeks of treatment
  - Response rates were comparable in null responders and partial responders
- ABT-450/r + ABT-333 + RBV for 12 weeks has the potential to achieve SVR in a high proportion of subjects without interferon

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