4-Week Virologic Response and Safety of ABT-450 Given with Low-dose Ritonavir (ABT-450/r) First As 3-Day Monotherapy Then in Combination with Pegylated Interferon Alpha-2a and Ribavirin (SOC) in Genotype 1 (GT1) HCV-infected Treatment-naïve Subjects

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Introduction

- ABT-450 is a potent acylsulfonamide protease inhibitor of the hepatitis C virus (HCV) identified as a lead compound by Abbott and Enanta, and being developed for the treatment of HCV genotype 1 infection in combination with other anti-HCV agents
- ABT-450 has inhibitory concentrations in the sub-nanomolar range in genotype 1a and 1b subgenomic replicon systems in the absence of human serum
- Ritonavir (RTV) co-administration boosted the pharmacokinetics of ABT-450 with ABT-450 C_{trough} and AUC increased 28- to 48-fold[1]; therefore, ABT-450 is being developed with low dose ritonavir (ABT-450/r) to enhance exposure and allow once-daily dosing
- ABT-450/r was safe and well tolerated in single and multiple dose studies in healthy volunteers[1, 2]
- We present here preliminary results at week 4 of the first study of ABT-450/r in HCV-infected subjects

Objective

- To analyze the efficacy and safety of various doses of once-daily ABT-450/r given alone for 3 days of monotherapy, followed by co-administration of ABT-450/r with standard of care (SOC) through 4 weeks of treatment

Methods

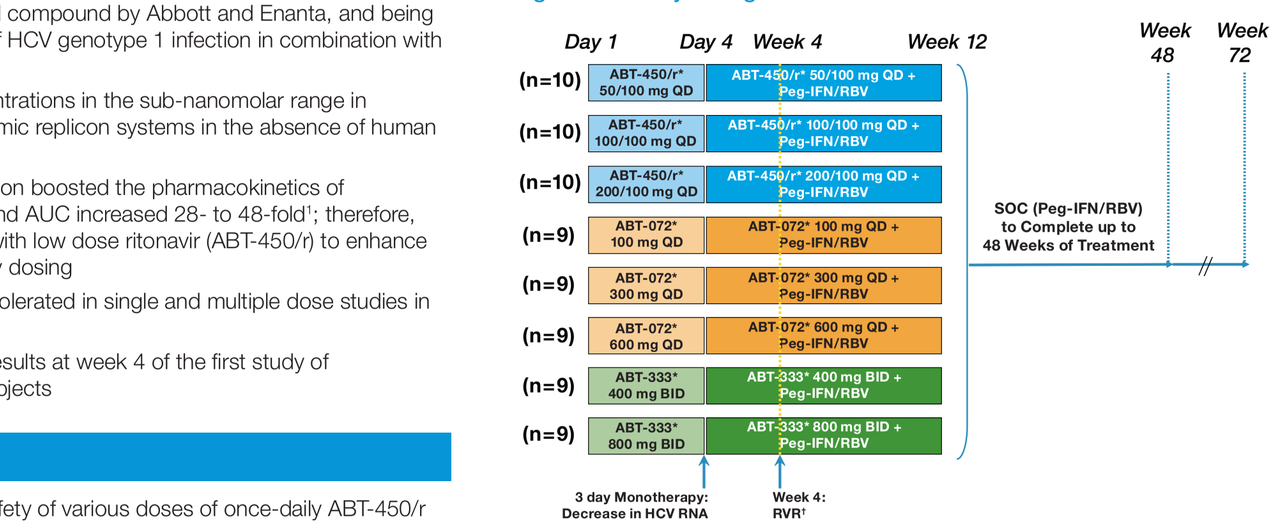
Study Design

- Study M11-602* is an on-going randomized, placebo-controlled, blinded (active *versus* placebo), dose ranging, phase 2a clinical trial. In this study, three cohorts of subjects were randomized to receive various doses of 1 of 3 direct acting antiviral (DAA) agents currently in clinical development: ABT-450/r, or one of 2 non-nucleoside polymerase inhibitors (ABT-072 or ABT-333). This study is fully enrolled.
- Data from the non-nucleoside polymerase inhibitor-containing arms will be presented elsewhere. We are presenting here the preliminary results from the first 4 weeks of treatment with ABT-450/r or placebo.
- To be eligible for enrollment in study M11-602, subjects had to meet the following inclusion criteria:
  - age 18 to 65 years
  - body mass index (BMI) ≥18 and <35 kg/m^2
  - chronic HCV genotype 1 infection for at least 6 months prior to study enrollment
  - plasma HCV RNA level ≥100,000 IU/mL at screening
  - liver biopsy within the past 3 years with histology consistent with HCV induced liver damage
- Exclusion criteria included:
  - liver biopsy with a METAVIR fibrosis score of 3 or 4
  - positive test result for hepatitis B surface antigen or anti-HIV antibodies
  - history of major depression within the 2 years prior to enrollment
  - unresolved clinically significant diseases other than HCV
- Subjects were randomized to one of 3 doses of ABT-450/r (50/100 mg, 100/100 mg or 200/100 mg) or placebo once daily for 3 days, followed by ABT-450/r or placebo in combination with standard of care (SOC) consisting of pegylated interferon alfa-2a 180 µg/week + weight-based ribavirin 1000-1200 mg/day through week 12. At week 12, ABT-450/r or placebo was discontinued and subjects received SOC alone through week 48 as shown in Figure 1.
- Subjects were confined to the study site from study day -1 until after the study procedures were completed on day 4. Subjects had subsequent out-patient study visits on days 5, 11, 18, and 28, and at weeks 6, 8, 10, and 12, followed by monthly visits from weeks 16 to 48 while on SOC treatment, then at weeks 52, 56, 60 and 72 during the follow-up period.
- Study procedures included monitoring of adverse events, physical examination, vital signs, 12-lead ECGs, and phlebotomy for analysis of pharmacokinetic parameters, HCV RNA level, and hematology and clinical chemistry testing

*The M11-602 study is registered with ClinicalTrials.gov, NCT01074008.

Methods, cont.

Figure 1. Study Design



*Placebo Controlled: n=2 placebo per ABT-450/r group and n=1 placebo per ABT-072 and ABT-333 group
†RVR: HCV <25 IU/mL (LOQ) at Week 4

Determination of Baseline Susceptibility to ABT-450

- HCV viral RNA was isolated from a baseline sample collected prior to the first dose of ABT-450/r, and the region of the virus encoding the NS3 protease domain was amplified by RT-PCR
- After cloning of this region into the appropriate HCV genotype 1a or 1b subgenomic replicon shuttle vector, EC_{50} values were determined using a transient transfection replicon assay with a firefly luciferase reporter
- Replicon reference strains were H77 and Con1 for genotypes 1a and 1b, respectively

Efficacy Analyses

- HCV RNA was measured using Roche COBAS TaqMan (LLOQ = 25 IU/mL and LLOD = 10 IU/mL)
- Virologic response was assessed as HCV RNA decrease from baseline in $\log_{10}$ IU/mL at each time point
- The study primary endpoint was the mean maximum decrease in HCV RNA during the 3-day monotherapy period (through day 4 predose), which was compared among ABT-450/r treatment groups and placebo using a one-way ANCOVA with treatment group as factor and baseline HCV RNA levels as covariate[3]
- The proportion of subjects with HCV RNA <25 IU/mL was assessed at week 4 (protocol-defined rapid virologic response, RVR)
- Pair-wise comparisons to placebo in mean change from baseline in HCV RNA to each time point though week 4 were performed using ANCOVA with treatment group as factor and baseline HCV RNA levels as covariate

Results

Subject Disposition and Baseline Characteristics

- A total of 24 HCV genotype 1-infected subjects were enrolled and randomized to 1 of 3 doses of ABT-450/r
- Eleven subjects in total in the study were randomized to receive placebo; all 11 are pooled in these analyses
- Four subjects discontinued study before week 4, none for DAA drug-related adverse events: one was lost to follow-up, two withdrew consent and one discontinued all treatment due to a severe adverse event of pain attributed to SOC
- Demographic and baseline characteristics were similar between groups (Table 1)
- 80% of subjects overall were infected with genotype 1a
- 89% of subjects overall had baseline HCV RNA >800,000 IU/mL

Results, cont.

Table 1. Demographic and Baseline Characteristics

Variable	Placebo N=11	ABT-450/r 50/100 mg N=8	ABT-450/r 100/100 mg N=8	ABT-450/r 200/100 mg N=8	ABT-450/r Total Active N=24
Age (years)					
Mean	51.5	48.4	50.9	50.6	50.0
Min-Max	44-60	33-59	48-55	29-57	29-59
Weight (kg)					
Mean	89.5	78.0	78.1	78.8	78.3
Min-Max	73-112	61-97	52-108	58-97	52-108
BMI (kg/m^2)					
Mean	28.8	25.7	26.9	27.1	26.6
Min-Max	25.1-33.4	21.2-29.6	18.7-33.2	21.2-32.5	18.7-33.2
Gender, n (%)					
Female	2 (18.2)	1 (12.5)	3 (37.5)	4 (50.0)	8 (33.3)
Male	9 (81.8)	7 (87.5)	5 (62.5)	4 (50.0)	16 (66.7)
Race, n (%)					
White	8 (72.7)	6 (75.0)	8 (100)	6 (75.0)	20 (83.3)
Black	3 (27.3)	1 (12.5)	0	2 (25.0)	3 (12.5)
Other	0	1 (12.5)	0	0	1 (4.2)
Ethnicity, n (%)					
Hispanic	1 (9.1)	4 (50.0)	3 (37.5)	3 (37.5)	10 (41.7)
Not Hispanic	10 (90.9)	4 (50.0)	5 (62.5)	5 (62.5)	14 (58.3)
HCV RNA ($\log_{10}$ IU/mL)					
Mean	6.86	6.60	6.75	6.88	6.74
Min-Max	5.13-7.47	5.21-7.21	5.65-7.36	5.75-7.49	5.21-7.49
Baseline HCV RNA, n (%)					
>800,000 IU/mL	10 (90.9)	7 (87.5)	7 (87.5)	7 (87.5)	21 (87.5)
HCV genotype, n (%)					
1a	9 (81.8)	7 (87.5)	5 (62.5)	7 (87.5)	19 (79.2)
1b	2 (18.2)	1 (12.5)	3 (37.5)	1 (12.5)	5 (20.8)

- Baseline phenotypic susceptibility of isolates from subjects randomized to ABT-450/r ranged from <1 to 5.7 times the EC_{50} of the reference strains (Table 2)

Table 2. Phenotypic Susceptibility to ABT-450 at Baseline (EC_{50} Compared with Reference Strains)

	Baseline EC_{50} Values (nM)		
	Range	Median	Reference
Genotype 1a (n=19)	0.45 – 5.72	0.87	1.03
Genotype 1b (n=5)	0.02 – 0.07	0.05	0.10

Efficacy Through Week 4

- The primary endpoint of the study was the mean maximum change in HCV RNA during the 3-day monotherapy with ABT-450/r or placebo. Through 3 days of monotherapy, response was similar in the 3 ABT-450/r dose groups: Mean maximum decreases from 3.89 to 4.11 $\log_{10}$ IU/mL were observed in all 3 dose groups compared to 0.36 $\log_{10}$ IU/mL for the placebo group (p<0.001 for each comparison)[3].
- Beginning at 8 hours post the first dose on day 1 through week 4, all 3 ABT-450/r dose groups had mean HCV RNA decreases from baseline statistically significantly different from placebo at every time point
- At week 4, the mean (± SD) HCV RNA decrease from baseline was 5.58 ± 0.65 $\log_{10}$ IU/mL for subjects on ABT-450/r *versus* 1.86 ± 1.90 $\log_{10}$ IU/mL for subjects on placebo (p<0.001)
- The mean HCV RNA (range) at week 4 was 1.15 (1.00 – 2.87) $\log_{10}$ IU/mL for subjects on ABT-450/r *versus* 4.97 (1.00 – 7.21) $\log_{10}$ IU/mL for subjects on placebo
- Through week 4, virologic response was similar in the 3 ABT-450/r dose groups (Figures 2 and 3)
- Although few subjects with genotype 1b enrolled, there were no apparent differences in virologic response to ABT-450/r or placebo between genotypes 1a and 1b
- No subject receiving ABT-450/r experienced a virologic rebound (increase ≥0.5 $\log_{10}$ IU/mL from nadir) through the 4 weeks of ABT-450/r + SOC treatment

Figure 2. Mean HCV RNA Change from Baseline by Dose Group Through Week 4 ($\log_{10}$ IU/mL)

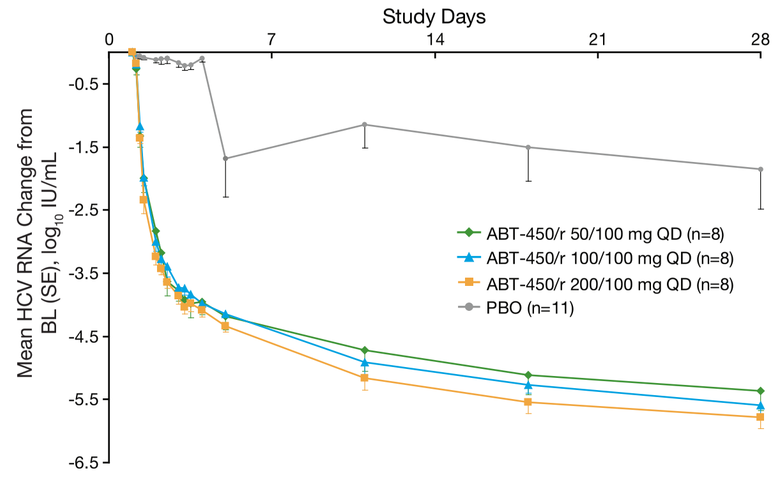


Figure 3. Mean HCV RNA by Dose Group from Baseline to Week 4

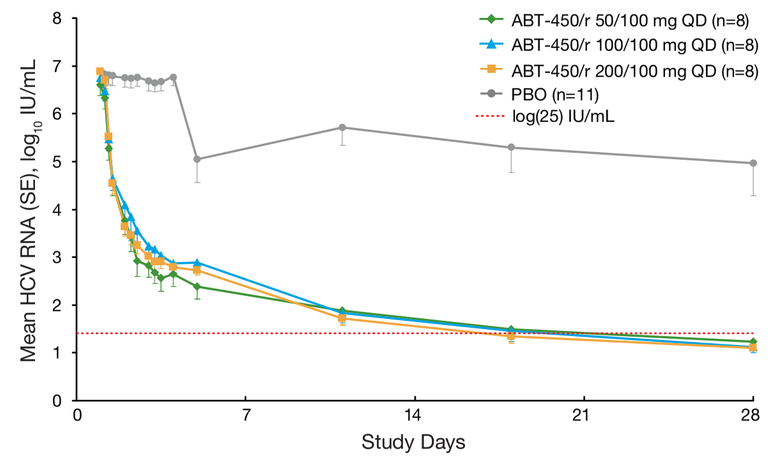


Table 3. Proportion of Subjects with HCV RNA <25 IU/mL at Week 4

	PBO	ABT-450/r 50/100 mg QD	ABT-450/r 100/100 mg QD	ABT-450/r 200/100 mg QD	TOTAL
N with Data at Week 4	11	8	7	8	23
n/N with HCV RNA <25 IU/mL (%)	1/8 (12.5)	7/8 (87.5)	6/7 (85.7)	8/8 (100)	21/23 (91.3)

- For each ABT-450/r dose group, mean HCV RNA was <25 IU/mL at week 4 (Figure 3)
- 21 of 23 (91.3%) subjects receiving ABT-450/r with data at week 4 had HCV RNA <25 IU/mL *versus* 1 out of 8 (12.5%) subjects receiving placebo (Table 3)
- In an Intent-to-Treat analysis, where discontinued subjects are counted as failures, 21/24 (87.5%) subjects randomized to ABT-450/r had HCV RNA <25 IU/mL *versus* 1/11 (9.1%) subjects randomized to placebo

Safety Results through Week 4

- No DAA drug-related severe adverse events were reported
  - One subject experienced severe pain in the neck, back and arms and discontinued study on day 4. This severe adverse event was attributed to SOC treatment.
- No subjects discontinued treatment for DAA drug-related adverse events
  - One subject discontinued from the study due to a severe adverse event of pain attributed to SOC
- Through week 4, the proportion of subjects experiencing at least one adverse event was comparable for subjects receiving ABT-450/r and those receiving placebo: 10/11 (91%) and 21/24 (87.5%) respectively
  - Most adverse events were mild
  - No statistically significant relationship between dose and frequency of adverse events was observed
- There were no statistically significant difference in frequency of adverse events reported by 2 or more subjects between ABT-450/r and placebo
- The most common adverse events included the following (ABT-450/r vs. placebo):
  - Headache: 54.2% vs. 36.4%
  - Diarrhea: 12.5% vs. 27.3%
  - Fatigue: 37.5% vs. 45.5%
  - Neutropenia: 12.5% vs. 27.3%
  - Nausea: 25.0% vs. 36.4%
  - Dizziness: 8.3% vs. 36.4%
  - Myalgia: 25.0% vs. 18.2%
- Adverse events of moderate severity considered possibly or probably related to ABT-450/r by the investigator in more than 2 subjects receiving ABT-450/r are
  - Headache: 12.5% ABT-450/r *versus* 9.12% placebo
  - Depression: 8.3% ABT-450/r *versus* 0% placebo
- There is no apparent increase in specific drug-related moderate adverse events with increasing ABT-450 dose
- Protocol-defined potentially clinically significant (PCS) laboratory abnormalities occurred infrequently with the exception of low neutrophil counts (ANC <1 x 10^9/L): 33.3% ABT-450/r *versus* 18.2% placebo)
  - Mean neutrophil counts at baseline were 3.626 x 10^9/L for subjects receiving ABT-450 r *versus* 4.275 x10^9/L for subjects receiving placebo
  - Through week 4, the mean change in neutrophil count was -1.870 x 10^9/L for subjects receiving ABT-450/r *versus* -2.964 x 10^9/L for subjects receiving placebo
  - Neutropenia was managed by reduction of the pegIFN dose
  - No subject discontinued treatment for neutropenia

Conclusions

- At week 4, the mean (± SD) HCV RNA decrease from baseline was 5.58 ± 0.65 $\log_{10}$ IU/mL for subjects on ABT-450/r compared with 1.86 ± 1.90 $\log_{10}$ IU/mL for subjects on placebo (P<0.001); the 3 doses showed similar HCV RNA decreases from baseline
- 21 of 23 (91.3%) subjects receiving ABT-450/r had HCV RNA <25 IU/mL at week 4 compared with 1 of 8 (12.5%) subjects on placebo
- ABT-450/r + SOC was safe and well tolerated during 4 weeks of treatment, with an adverse event profile comparable to SOC alone

References

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3. Lawitz E. et al. Initial antiviral activity of the HCV NS3 protease inhibitor ABT-450 when given with low dose ritonavir as 3-day monotherapy: Preliminary results of study M11-602 in genotype 1 (GT1) HCV-infected treatment-naïve subjects. 61st Annual Meeting of the AASLD, Boston, 2010; Abstract #1855.

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Disclosures

I. Gaultier, D. Cohen, R. Menon, L.M. Larsen, T. Podsadecki, and B. Bernstein are Abbott employees and may hold Abbott stock or options. E. Lawitz, F. Poordad, E. DeJesus, K.V. Kowdley, and G. Sepulveda are investigators in this study. E. Lawitz and F. Poordad are also consultants to Abbott.