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

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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_{max} 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 of the first study of ABT-450/r in HCV-infected subjects

Objective

- To analyze the efficacy and safety of various doses of ABT-450/r given once daily as monotherapy for three days

Methods

Study Design

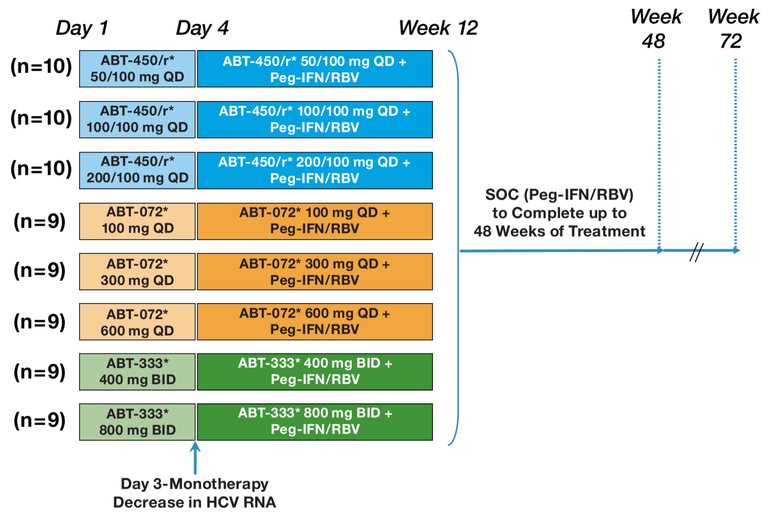
- Study M11-602 is an on-going randomized, placebo-controlled, blinded (active *versus* placebo), dose ranging, phase 2a clinical trial. In this study, three cohorts of subjects were randomized to receive various doses of one of three direct acting antiviral (DAA) agents currently in clinical development: 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 monotherapy 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

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

Methods, cont.

- 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
- 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

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.

Pharmacokinetic Evaluations

- ABT-450 and RTV concentrations were determined using a liquid chromatography tandem mass spectroscopic method (LC-MS/MS) with a lower limit of quantitation of 0.5 ng/mL
- Pharmacokinetic and statistical analysis was conducted using WinNonlin Professional version 5.2 (Pharsight Corporation, CA)

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 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 level as covariate

Results

Baseline Characteristics and Subject Disposition

- A total of 24 HCV genotype 1 infected subjects were enrolled and randomized to one of three doses of ABT-450/r (Table 1)
- Eleven subjects in total in the study were randomized to receive placebo; all 11 are included in these analyses
- No subjects discontinued during the 3-day monotherapy treatment
- Demographic and baseline characteristics were similar between groups (Table 1)
- 80% subjects overall were infected with genotype 1a
- 89% subjects overall had HCV RNA >800,000 IU/mL at baseline

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)

Pharmacokinetics

- Figure 2 presents the mean (±SD) ABT-450 plasma concentrations during the 72 hours of monotherapy by dose group

Figure 2. PK—Mean (± SD) ABT-450 Plasma Concentrations for the First 72 Hours by Dose Group

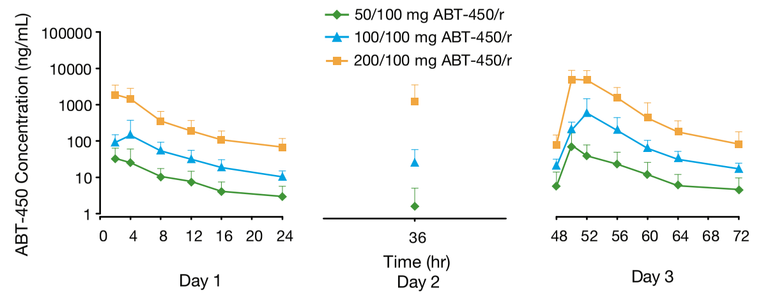


Table 2 presents the key pharmacokinetic parameters for ABT-450, on the first and the third day of monotherapy

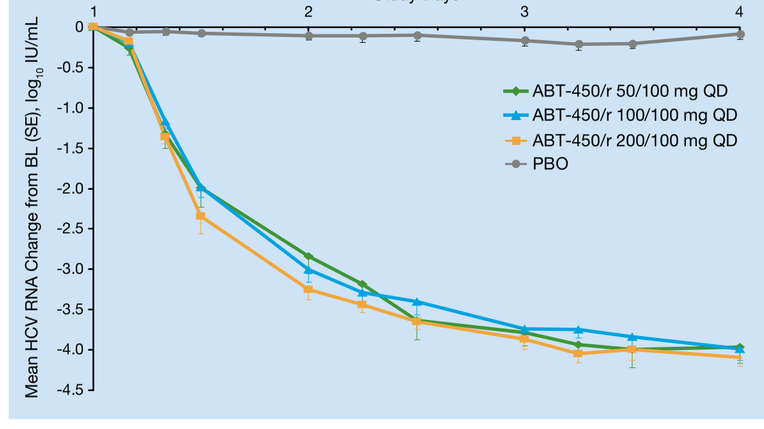
- As observed in healthy subjects, there is a more than dose-proportional increase in ABT-450 exposure
- Mean ABT-450 C_{max} and AUC values were higher in HCV-infected subjects compared with healthy subjects[1, 2]

Table 2. Mean (%CV) ABT-450 Pharmacokinetic Parameters During 3-day Monotherapy Treatment

	ABT-450 Dose (N)	50/100 mg QD (N=8)*	100/100 mg QD (N=8)*	200/100 mg QD (N=6)†
Day 1	C_{max}	34 (92)	164 (135)	2251 (72)
	C_{max}/Dose	0.69	1.64	11.26
	AUC_{24}	248 (99)	1114 (90)	11130 (75)
	AUC_{24}/Dose	4.95	11.14	55.65
	T_{max}	2.5 (37)	4.8 (74)	2.7 (39)
	C_{trough}	3 (83)	10 (45)	61 (76)
Day 3	C_{max}	77 (117)	620 (136)	5848 (69)
	C_{max}/Dose	1.54	6.20	29.24
	AUC_{24}	469 (97)	3490 (115)	33705 (78)
	AUC_{24}/ Dose	9.37	34.90	168.53
	T_{max}	2.3 (35)	3.7 (22)	3.0 (38)
	C_{trough}	5 (109)	17 (42)	82 (117)

*PK data available for N=6 at Day 3; †for N=4 at Day 3.

Figure 3. Mean HCV RNA Mean (SE) Change from Baseline by Dose Group During 3-day Monotherapy



Efficacy

- 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
- Profound decreases in HCV RNA were observed at all ABT-450/r doses during the 3-day monotherapy (Figure 3 and Table 3)
- From day 1 through day 4, the mean maximum HCV RNA decrease from baseline was 4.02 $\log_{10}$ IU/mL (SD = 0.43) for subjects receiving ABT-450/r *versus* 0.36 $\log_{10}$ IU/mL (SD = 0.13) for subjects receiving placebo (P<0.001)
- Similar HCV RNA changes from baseline were observed in the 3 ABT-450/r dose groups

Table 3. Mean Maximum HCV RNA Change from Baseline During 3-day Monotherapy, and Mean HCV RNA on Day 4 Predose ($\log_{10}$ IU/mL)

	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	11	8	8	8	24
Mean max HCV RNA change (range)	-0.36 (-0.18;-0.63)	-4.07 (-3.51; -5.21)	-3.89 (-3.24; -4.35)	-4.11 (-3.77; -4.70)	-4.02 (-3.24; -5.21)
P-value* *versus* PBO		<0.001	<0.001	<0.001	<0.001
Mean HCV RNA on day 4 predose (range), $\log_{10}$ IU/mL	6.78 (5.30-7.47)	2.64 (1.40-3.32)	2.87 (2.28-3.71)	2.80 (1.83-3.21)	2.77 (1.40-3.71)

*P-value from an ANCOVA with baseline value as the covariate and with treatment group as factor.

Safety Results

- There were no treatment-emergent serious adverse events (SAEs)
- The proportion of subjects experiencing at least one treatment-emergent adverse event was similar for those receiving ABT-450 compared with those receiving placebo (10/24 [41.7%] *versus* 5/11 [45.5%], respectively). Reported adverse events were similar across ABT-450/r dose groups.
- Adverse events reported by more than 1 subject overall included dizziness (2/24 *versus* 3/11), headache (5/24 *versus* 0/11) and somnolence (1/24 *versus* 1/11) in subjects receiving ABT-450/r or placebo, respectively
- All except two adverse events were mild
  - Two subjects receiving ABT-450/r (1 each in the ABT-450/r 50/100 mg and 200/100 mg groups) experienced headache of moderate severity on day 1; both were treated with acetaminophen
- There were no reports of severe adverse events
- A Grade 3 low neutrophil count (0.93 x10^9/L) was observed on day 4 in one subject receiving ABT-450/r 200/100 mg (day 1 predose value = 1.27 x10^9/L)
- No other clinically significant hematology or chemistry values were observed

Conclusions

- ABT-450/r resulted in a profound decrease in HCV RNA during 3 days of monotherapy at all doses studied
- Through 3 days of monotherapy response was similar in the 3 ABT-450/r dose groups. The mean maximum HCV RNA decrease from baseline was 4.02 $\log_{10}$ IU/mL (SD=0.43) for subjects receiving ABT-450/r *versus* 0.36 $\log_{10}$ IU/mL (SD = 0.13) for subjects receiving placebo (P<0.001).
- ABT-450/r was safe and well tolerated when taken as monotherapy for 3 days, and no subjects discontinued during the monotherapy period

References

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Disclosures

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