



## 2.0 Synopsis

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> ABT-333		
<b>Name of Active Ingredient:</b> Sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide		
<b>Title of Study:</b> A Blinded, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of Multiple Doses of ABT-333 Alone and in Combination with Pegylated Interferon (pegIFN) and Ribavirin (RBV) in Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection		
<b>Investigator:</b> Eric Lawitz, MD		
<b>Study Sites:</b> Six investigators at 6 sites in the United States, including Puerto Rico		
<b>Publications:</b> One abstract		
<b>Studied Period (Years):</b> First Subject First Visit: 16 March 2009 Last Subject Last Visit: 10 July 2009	<b>Phase of Development:</b> 2a	
<b>Objectives:</b> The primary objective of this study was to assess the safety, tolerability, pharmacokinetics, and antiviral activity of multiple oral doses of ABT-333 or placebo when administered as monotherapy for 2 days, followed by coadministration of ABT-333 or placebo with the pegIFN and RBV combination therapy for 26 days in treatment-naïve HCV-infected subjects.  The secondary objective of this study was to assess emergence of resistant virus in conjunction with kinetics of viral load decay and rebound in treatment-naïve HCV-infected subjects.		
<b>Methodology:</b> Study M10-380 was a Phase 2a, blinded, randomized, multicenter, multiple-dose, placebo-controlled study designed to assess the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-333 versus placebo in HCV genotype 1-infected treatment-naïve subjects.  The total duration of treatment in Study M10-380 was 28 days. In addition, there was a screening period of up to 30 days prior to start of treatment, and a follow-up period of 14 additional days after the last treatment with ABT-333 or placebo was administered. ABT-333 or placebo were administered orally, first as monotherapy for 2 days and then in combination with the standard of care (SOC) therapy of pegIFN and RBV for 26 days. The study was to involve 2 sequential evaluations, Part 1 and Part 2, enrolling approximately 68 subjects overall (30 in Part 1 and 38 in Part 2). Part 1 was designed to test ABT-333 doses of up to 1200 mg per day, and Part 2 was to test ABT-333 doses of 2400 to 3200 mg per day.		



**Methodology (Continued):** Thirty subjects meeting inclusion and not meeting exclusion criteria were planned and enrolled in Part 1 of the study. At the Day –1/Baseline Visit, subjects in Part 1 who met the enrollment criteria were randomized to 1 of 6 treatment groups in 1 of 3 arms. Each arm contained 8 subjects receiving ABT-333 (300 mg twice daily [BID], 600 mg BID, or 1200 mg once daily [QD]) and 2 placebo subjects. The placebo subjects were combined into a single group for purposes of analysis. For all groups, the pegIFN dose was 180 µg subcutaneously once a week and the RBV total daily dose was 1000 to 1200 mg orally divided BID (adjusted based on body weight).

Subjects were confined to the study site and supervised during the lead-in monotherapy period, beginning on Study Day –1 and ending on Study Day 3. Subjects returned for observed morning dosing on Study Days 4 and 5, and then for study follow-up visits on Study Days 10, 17, 24, 28 (or discontinuation), and on Day 42 on an outpatient basis for additional study procedures. Additionally, if felt medically appropriate, subjects who received at least 1 dose of study drug or matching placebo also received up to 44 additional weeks of SOC therapy following study completion or discontinuation.

Thirty-eight subjects were to be administered ABT-333 at daily doses of 2400 to 3200 mg in Part 2 of the study. Per the protocol, Part 2 could be cancelled, or the planned doses could be modified, after the evaluation of the safety, antiviral activity, and available pharmacokinetic data from Part 1 of this study and/or from 2 additional ongoing Abbott studies with ABT-333. Part 2 of the study was not performed, because initial review of safety and efficacy in Part 1 showed similar response rates across all 3 ABT-333 doses studied. Therefore, the analysis of safety, antiviral activity, tolerability, and pharmacokinetic data following Part 1 was the final analysis, rather than the planned interim analysis.

**Number of Subjects (Planned and Analyzed):** A total of 68 subjects were to be enrolled in the study (30 subjects in Part 1 and 38 subjects in Part 2). Thirty subjects were enrolled, dosed, and analyzed in Part 1. Twenty-nine subjects completed the treatment; 1 subject was lost to follow-up on Day 17 but was still included in all analyses for which data were available. Based on the results from Part 1, Part 2 was not conducted, and no subjects were enrolled.

**Diagnosis and Main Criteria for Inclusion:** Subjects were HCV-infected, treatment-naïve adults 18 to 70 years of age, with a BMI of 18 to 35. Females were either postmenopausal for at least 2 years or surgically sterile. Male subjects and/or partner(s) had to be practicing 2 effective methods of birth control. Subjects were in a condition of general good health, other than the HCV infection. Subjects had a chronic HCV genotype 1 infection for at least 6 months prior to study enrollment with no evidence of cirrhosis or liver pathology due to any cause other than chronic HCV. Subjects had plasma HCV RNA levels > 50,000 IU/mL at Screening. Subjects could not have previously received any investigational anti-HCV agents, IFN, pegIFN, or RBV.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:** For Part 1 of the study, ABT-333 was provided in 50 mg capsules for oral administration (bulk lot number 08-019531). Subjects received ABT-333 doses of 300 mg BID, 600 mg BID, or 1200 mg QD. For Part 2, ABT-333 was to be provided in 400 mg tablets; however, Part 2 was not conducted.

Both RBV (COPEGUS®) and pegIFN (PEGASYS®) were purchased from Roche. RBV was provided in 200 mg tablets and was to be administered orally with food (bulk lot number 08-020679); subjects received 1000 to 1200 mg of RBV daily divided BID. PegIFN was provided in syringes containing a concentration of 180 µg drug/0.5 mL for subcutaneous injections (bulk lot number 08-020657); the drug was administered weekly.



**Duration of Treatment:** The total duration of treatment was 28 days. ABT-333 or placebo was administered as monotherapy for 2 days, followed by coadministration of ABT-333 or placebo with the SOC therapy (pegIFN and RBV) for 26 days.

**Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:**

The placebo for ABT-333 was provided as a capsule to be taken orally; it contained 0 mg of ABT-333 (bulk lot number 05-001846). Subjects received the number of capsules that matched the ABT-333 dose in the arm into which they were randomized.

**Criteria for Evaluation**

**Efficacy:** The mean maximal decrease from baseline in HCV RNA during monotherapy treatment (through prior to Day 3 morning dose) and during treatment (through Day 28) were both considered primary endpoints. Subgroup analyses for primary endpoints included subgroups of HCV genotype, race, ethnicity, sex, age, baseline HCV RNA levels, and weight.

The following efficacy endpoints were considered secondary:

- The mean change from baseline in  $\log_{10}$  HCV RNA to each time point during the treatment period
- The fold change in concentration required for 50% effect ( $EC_{50}$ ) levels at each postbaseline time point compared with baseline and reference samples
- The percentage of subjects with at least a 2  $\log_{10}$  maximal decrease in HCV RNA levels during the treatment period
- The percentage of subjects with HCV RNA levels  $\leq 25$  IU/mL (lower limit of quantitation [LLOQ]) or  $\leq 10$  IU/mL (lower limit of detection [LLOD]) on Day 28 or at the Final Visit

In addition, the most prevalent mutations in HCV polymerase sequence from subject isolates associated with resistance to study drug were summarized.

**Pharmacokinetic:** Plasma concentrations of ABT-333 and its metabolite, RBV, and serum concentrations of IFN were measured for each subject. The pharmacokinetic parameter values of ABT-333 and its metabolite after the morning dose on Day 1 were estimated using noncompartmental methods. These included: the maximum plasma concentration ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), and area under the plasma concentration-time curve from 0 to 12 hours post dose ( $AUC_{12}$ ).

**Safety:** Adverse events, clinical laboratory determinations, vital signs, and electrocardiograms were summarized for each subject.

**Statistical Methods**

**Efficacy:** The maximal decrease during monotherapy was the change from baseline to the lowest  $\log_{10}$  HCV RNA anytime after the first dose of study drug on Day 1 through the last  $\log_{10}$  HCV RNA before the first dose of study drug on Day 3. The maximal decrease during treatment was the change from baseline to the lowest  $\log_{10}$  HCV RNA after the first dose of study drug on Day 1 through the last  $\log_{10}$  HCV RNA on Day 28. For each treatment group, both endpoints were summarized descriptively using N, mean, median, standard deviation, and range. For each endpoint, the maximum decrease was summarized and compared between treatment groups using contrasts within a 1-way ANCOVA, with treatment group as the factor and  $\log_{10}$  baseline HCV RNA level as the covariate.



### Statistical Methods (Continued):

**Efficacy (Continued):** The mean change in HCV RNA (in  $\log_{10}$  IU/mL) from baseline (prior to dosing on Study Day 1) to each time point after the first dose and the final visit was summarized and compared between treatment groups by a 1-way ANCOVA, with treatment as the factor and baseline  $\log_{10}$  HCV RNA level as the covariate.

The percentage of subjects with  $\geq 2 \log_{10}$  decrease from baseline in HCV RNA at some time point during the treatment period and the percentage of subjects with HCV RNA levels  $\leq 25$  IU/mL and  $\leq 10$  IU/mL on Day 28 or at the final visit were compared among treatment groups using Fisher's exact test. For all HCV RNA analysis, the baseline value was the last measurement before the first dose on Day 1 and data more than 1 day post dosing was excluded.

The development of resistance during monotherapy and during treatment was assessed by calculating the fold change in  $EC_{50}$  levels at each postbaseline time point compared both to baseline and prototypic standards. The fold changes at each time point were summarized descriptively.

**Pharmacokinetic:** An analysis of covariance (ANCOVA) was performed on  $T_{max}$  and dose-normalized  $C_{max}$  and  $AUC_{12}$  of ABT-333 and its metabolite to investigate questions of dose proportionality on Day 1. The logarithmic transformation was used for  $C_{max}$  and  $AUC_{12}$ . Subjects were classified by dose level. Body weight, sex, and other variables (e.g., smoking status and age) were included in the model if the regression coefficient was significant at level 0.10. Within the modeling framework, the highest and lowest doses were compared.

To address the effect of pegIFN and RBV on pharmacokinetics of ABT-333, analyses were performed on  $C_{trough}$  of ABT-333 and its metabolite. The natural logarithmic transformation was used for  $C_{trough}$ . The change in  $C_{trough}$  occurring between administration of ABT-333 alone ( $C_{trough}$  on Day 3, prior to the first dose of combination therapy) and concomitant administration of ABT-333 plus pegIFN and RBV ( $C_{trough}$  on Day 4) was analyzed by a paired t test. Similarly, a paired t test was performed on the Hour-4 concentrations collected on Days 1 and 3.

Additionally, a repeated measures analysis was performed on pegIFN concentrations of Days 4 and 5. The model included effects for regimen, day and regimen-day interaction. The same analysis was done for RBV trough concentrations on Days 4 and 5.

**Safety:** For the safety endpoints of adverse events, clinical laboratory tests, and vital signs, pairwise comparisons between each ABT-333 dose group and the placebo group were made. All subjects who received at least 1 dose of study medication were included in the safety analyses.

The number and percentage of subjects in each treatment group having treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA Version 12.0) primary System Organ Class and preferred term and compared among treatment groups using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events was also provided, with further breakdowns by severity rating and relationship to study drug. Subjects reporting more than 1 adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than 1 type of event within a System Organ Class were counted only once for that System Organ Class.



### Statistical Methods (Continued):

**Safety (Continued):** Clinical laboratory tests were summarized by treatment group at each visit. The baseline value was the last measurement prior to the initial dose of study drug. Mean changes from baseline to each postbaseline visit were summarized and treatment group differences for mean changes from baseline were analyzed using ANOVA with treatment group as the factor. Laboratory data values were categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percent of subjects who experienced postbaseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized by treatment group. In addition, the number and percentage of subjects with postbaseline values meeting prespecified criteria for potentially clinically significant laboratory values were summarized by treatment group, and pairwise comparisons between the treatment groups were made with Fisher's exact test.

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each postbaseline visit were summarized descriptively and treatment group differences were analyzed using ANOVA with treatment group as factor. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for potentially clinically significant vital signs values were summarized. Comparisons of the percentage of subjects who experienced a value meeting the criteria between treatment groups were performed using Fisher's exact test.

### Summary/Conclusions

Study M10-380 was a blinded, randomized, multiple-dose, placebo-controlled study designed to assess the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-333 versus placebo in HCV genotype 1-infected treatment-naïve subjects. In this study, ABT-333 or placebo were first administered as monotherapy for 2 days and then in combination with the SOC therapy of pegIFN and RBV for 26 days. Three doses of ABT-333 (300 mg BID, 600 mg BID, and 1200 mg QD) were assessed based on previous multiple-dose studies of ABT-333 in healthy volunteers and HCV-infected treatment naïve subjects. A planned second part of the study utilizing higher doses of ABT-333 was not performed, because initial review of safety and efficacy in Part 1 showed similar response rates across all 3 doses studied.

**Efficacy Results:** Three doses of ABT-333 (300 mg BID, 600 mg BID, and 1200 mg QD) or placebo were administered as monotherapy through prior to Day 3 morning dose, and in combination with pegIFN and RBV from Day 3 through Day 28. Overall, in both the primary and secondary efficacy measurements, ABT-333 was superior to placebo; and a greater antiviral activity was observed with all 3 doses of ABT-333 in combination with pegIFN and RBV than with pegIFN and RBV alone. No clear dose-response relationship was observed between the 3 treatment groups.

The primary efficacy variables were the mean maximum decrease from baseline in HCV RNA during monotherapy treatment (through prior to Day 3 morning dose) and during treatment (through Day 28). There was a statistically significantly greater decrease in HCV RNA from baseline through prior to Day 3 morning dose in the ABT-333-combined group versus the placebo group (LS mean nadir change:  $-0.26 \log_{10}$  IU/mL in the placebo group versus  $-0.82 \log_{10}$  IU/mL in the ABT-333 combined group,  $P = 0.024$ ). The LS mean changes were similar between the 3 ABT-333 groups (LS mean change of  $-1.01$ ,  $-0.78$  and  $-0.68 \log_{10}$  IU/mL for the 300 mg BID, 600 mg BID and 1200 mg QD groups, respectively).



**Summary/Conclusions (Continued):**

**Efficacy Results (Continued):** Overall, there was a statistically significantly greater mean maximum decrease from baseline through Day 28 in the ABT-333 combined group versus the placebo group (LS mean nadir change:  $-1.37 \log_{10}$  IU/mL for the placebo group versus  $-3.73 \log_{10}$  IU/mL for the ABT-333 combined group,  $P = 0.001$ ). There was little difference between the 3 ABT-333 dose groups and the maximum change in HCV RNA from baseline through Day 28 was statistically significantly greater for each ABT-333 dose groups compared with the placebo group (LS mean nadir changes:  $-1.37$  for the placebo group versus  $-3.65$ ,  $-3.96$ , and  $-3.59 \log_{10}$  IU/mL for the 300 mg BID, 600 mg BID, and 1200 mg QD dose groups, respectively).

Secondary efficacy variables also demonstrated that ABT-333 in combination with pegIFN and RBV was superior to placebo in combination with pegIFN and RBV. All 3 ABT-333 dose groups demonstrated statistically significant differences in HCV RNA decrease compared to the placebo group from baseline to Days 10, 17, and 24, and the ABT-333 300 mg BID and 600 mg BID dose groups and the combined ABT-333 dose group demonstrated statistically significant differences in HCV RNA decrease compared to the placebo group from baseline to Day 28. On Day 28, the LS mean changes from baseline (SE) were  $-1.45$  (0.68)  $\log_{10}$  IU/mL for the placebo group versus  $-3.65$  (0.53,  $P = 0.018$ ),  $-3.67$  (0.57,  $P = 0.020$ ), and  $-3.53$  (0.31,  $P = 0.009$ )  $\log_{10}$  IU/mL for the ABT-333 300 mg BID and 600 mg BID dose groups and the combined ABT-333 group, respectively. No clear dose-response relationship was observed between the 3 treatment groups during the 28 days of dosing (2 days of monotherapy followed by 26 days of ABT-333 in combination with pegIFN and RBV).

Overall, among all ABT-333-treated subjects, 79.2% of the subjects (19 of 24) had at least a 2  $\log_{10}$  maximal decrease in HCV RNA, 41.7% of the subjects (10 of 24) had HCV RNA levels  $\leq$  LLOQ (25 IU/mL) and 16.7% of the subjects (4 of 24) had HCV RNA levels  $\leq$  LLOD (10 IU/mL).

The development of resistance to ABT-333 was measured during the study. Twenty four of 29 samples (representing 16 subjects) showed a greater than 10-fold loss of susceptibility to ABT-333 relative to the initial value for that subject. Each of these samples contained variants at 1 or more of the 5 signature positions (amino acids previously identified to contain common resistant variants) of the NS5B polymerase gene. Three of the 5 subjects accounting for the remaining samples had, at a later time point, a sample with detectable levels of resistant variants at amino acid 559. Variants were also noted in samples with smaller losses of susceptibility. However, sequencing of mixed populations of molecules does not give sufficiently quantitative results to determine whether the difference in loss of susceptibility is due to the relative prevalence of the variants or due to an association with variants elsewhere in the gene.

While nearly all of the samples that accumulated resistance to ABT-333 also carried known resistance mutations, those mutations did not appear to be a significant factor in determining the extent of viral load decrease. When the distribution of resistant variants was compared with the minimum HCV RNA levels for each subject, of the 17 subjects in whom resistant variants were detected, 8 had nadir HCV RNA levels of less than 1000 IU/mL, and 8 had minimum HCV RNA levels that exceeded 1000 IU/mL. Nine of 13 subjects lacking detectable resistance variants had minimum HCV RNA levels of less than 1000 IU/mL. Thus, while significant levels of resistance were detected in the replicon-based assay, the genetic resistance variants were distributed across dosage groups and across subsets of viral load decrease and phenotypic resistance. The emergence of resistant variants on treatment with ABT-333 did not appear to impact continued response to therapy, suggesting that resistant variants are still susceptible to the combination of ABT-333 plus pegIFN and RBV.



**Summary/Conclusions (Continued):**

**Efficacy Results (Continued):** The amino acid sequences of multiple clones of the NS5B gene were determined from selected samples. Variant-containing clones were detected in 22 of 24 subjects administered ABT-333. The percentage of clones encoding a resistance-conferring variant at 1 or more of the 5 signature positions increased on Day 10 and at later timepoints. The predominant amino acid substitutions at the positions examined were C316Y; M414T>I,V; Y448C; Y448H; S556G; and D559 G>N. These were also the predominant substitutions noted at these positions in in vitro assays.

**Pharmacokinetic Results:** ABT-333 exposure in treatment-naïve HCV-infected subjects increased with increasing doses. The trough concentrations indicated that pegIFN and RBV coadministration did not affect ABT-333 pharmacokinetics.

The HCV RNA decline following administration of ABT-333 in combination with pegIFN and RBV was described using an exposure response model. All doses administered in Study M10-380 (300 mg BID, 600 mg BID, and 1200 mg QD) appear to have achieved similar response rates both for ABT-333 monotherapy and for ABT-333 in combination with the SOC. Combination of ABT-333 with pegIFN and RBV resulted in a synergistic effect on HCV RNA decline. The baseline in vitro EC<sub>50</sub> was a significant covariate in HCV RNA decline.

**Safety Results:** At least 1 treatment-emergent adverse event was reported for all 24 subjects (100%) receiving ABT-333, and for 5 of 6 subjects (83.3%) receiving placebo. The majority of adverse events reported for ABT-333 were mild or moderate in severity. No subjects discontinued the study due to an adverse event, and no serious adverse events or deaths were reported.

The most commonly reported adverse events in subjects receiving ABT-333, regardless of severity and relationship to study drug, were headache (58.3% versus 33.3% in the placebo group); fatigue (29.2% versus 16.7% in the placebo group); influenza-like illness (25.0% versus 50.0% in the placebo group); nausea (25% versus 0% in the placebo group), anemia (20.8% versus 0% in the placebo group), arthralgia (16.7% versus 16.7% in the placebo group), chills and pyrexia (16.7% versus 0% in the placebo group for each), depression (12.5% versus 16.7% in the placebo group), and neutropenia and cough (12.5% versus 0% in the placebo group for each).

Of the most frequent treatment emergent adverse events that occurred approximately twice as commonly in the ABT-333 dose group than in the placebo group (anemia, chills, pyrexia, neutropenia, and cough), most were attributed by the investigator to pegIFN and/or RBV therapy.

The most common adverse events (> 10%) in the ABT-333 group that were considered by the investigator to be possibly or probably related to the administration of study drug that were reported for subjects in the ABT-333 group were headache and nausea; two thirds of these headache and nausea events were also considered by the investigator to be related to the SOC (both pegIFN and RBV). The majority of all adverse events reported in the study were assessed by the investigator to be possibly or probably related to pegIFN and RBV rather than treatment with ABT-333 or placebo.

The majority of adverse events reported in the study were mild or moderate in severity. Only 1 subject (4.2%) in the ABT-333 group, and no subjects in the placebo group, experienced a severe adverse event (neutropenia). Adverse events of neutropenia were reported in 3 subjects in the ABT-333 group (2 moderate events and 1 severe event), and were considered by the investigator to be probably not related or not related to ABT-333 and RBV, and probably related to pegIFN. Two of the neutropenia events (in 2 subjects) were managed with pegIFN dose reductions; the subjects' neutrophil counts stabilized but remained low.



**Summary/Conclusions (Continued):**

**Safety Results (Continued):** Potentially clinically significant (PCS) low neutrophil counts were reported in the ABT 333 treatment group only (6 subjects). In 3 of the 6 subjects, the PCS low neutrophil counts were associated with adverse events of neutropenia (2 moderate and 1 severe), all of which were considered by the investigator to be probably related to pegIFN and probably not or not related to ABT-333 and RBV. All of the PCS low neutrophil counts occurred after initiation of pegIFN therapy, with onset days ranging from Day 10 (7 days after initiation of pegIFN therapy) to Day 42 (14 days after discontinuation of ABT-333). In spite of the unbalanced distribution of PCS low neutrophil counts observed, there was no apparent difference in mean change from baseline in neutrophil counts between any ABT-333 treatment group and the placebo group. In addition, the mean change from baseline did not appear to differ between the last day of ABT-333 treatment and the Day 42 follow-up study visit, when subjects were receiving pegIFN and RBV alone. ABT-333 therapy was not interrupted in any subject, although the pegIFN dose was adjusted for 2 of the subjects (including the severe case) and 1 subject was treated with granulocyte-colony stimulating factor. The neutrophil counts stabilized or improved for all subjects by Final Study Visit. For these reasons, the very low neutrophil counts occurring in this study seem more likely related to pegIFN therapy than to ABT-333.

Statistically significant differences in mean change from baseline compared to placebo were observed in total and direct bilirubin, even though no clinically significant increases in bilirubin were observed for any subject. Other chemistry parameters showed only sporadic statistically significant differences in mean change from baseline compared to placebo at isolated time points. Treatment-emergent onset of all other abnormal laboratory parameters was sporadic, with no apparent trend or pattern.

**Conclusions:** The results of Study M10-380 indicate that ABT-333 appears to be safe and well tolerated when administered for 28 days to HCV-infected, treatment-naïve adult subjects in combination with pegIFN and RBV. Addition of ABT-333 to pegIFN and RBV is associated with statistically significantly greater maximal decreases in HCV RNA level in 28 days compared with pegIFN and RBV alone. These results support further study of ABT-333 for the treatment of chronic hepatitis C infection.