2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-450, ritonavir, ABT-267, ribavirin, pegylated interferon		
Name of Active Ingredient: ABT-450, Ritonavir, ABT-267, Ribavirin, Pegylated interferon		

Title of Study:

An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon α-2a and Ribavirin (PegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study

Coordinating Investigator: David Bernstein, MD

Study Sites: A total of 23 sites enrolled subjects in Argentina, Australia, Hungary, Poland, Romania, Slovakia, Spain, the United Kingdom, and the United States.

Publications: None

Studied Period (Years): First Subject First Visit: 18 December 2012 Last Subject Last Visit: 03 May 2017	**Phase of Development:** 2

Objectives:

The primary objective of this study was to evaluate the safety and antiviral efficacy defined as the percentage of subjects with sustained virologic response 12 weeks post-dosing (SVR_{12}; HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after the last dose of study drug).

The secondary objectives of this study were to 1) evaluate the percentage of subjects with sustained virologic response 24 weeks post-dosing (SVR_{24}; HCV RNA < LLOQ 24 weeks after the last dose of study drug) and 2) evaluate the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA < LLOQ at Weeks 4 through 12 of therapy with ABT-450/r plus ABT-267 plus PegIFN/RBV).

Methodology:

This was a Phase 2, open-label, single-arm combination treatment study of ABT-450/r and ABT-267 in combination with PegIFN/RBV in HCV GT1-infected subjects (including subjects with compensated cirrhosis) who had experienced virologic failure while participating in a previous AbbVie/Abbott DAA combination study. Among subjects who previously experienced null or partial response to PegIFN/RBV treatment at any time prior to pre-screening for this study, or who experienced any prior failure with PegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, enrollment in this study was restricted to those in whom population sequencing at the Pre-screening Visit did not detect the presence of variants relative to the appropriate prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following amino acid positions: NS3 155, 156, or 168; or NS5A 28, 29, 30, 31, 32, 58, or 93. All other subjects were allowed to enroll in Study M13-101 at the discretion of the investigator, regardless of whether variants at any of these amino acid positions were detected.

This study consisted of a pre-screening period, a screening period, and 3 sequential study parts (identified as substudies in the protocol:

- Substudy 1 (Treatment Intensification [TI]): 24 weeks of therapy with ABT-450/r plus ABT-267 plus PegIFN/RBV;
- Substudy 2 (PegIFN + RBV Treatment): 24 weeks of PegIFN/RBV therapy alone;
- Substudy 3 (Post-treatment [PT] Follow-up Period): 48 weeks after last dose of any study drug for resistance monitoring and HCV RNA viral load testing

Number of Subjects (Planned and Analyzed):

Approximately 35 subjects were planned; 32 subjects were enrolled; all received at least 1 dose of study drug and were analyzed.

Diagnosis and Main Criteria for Inclusion:

Subject must have been HCV GT1 infected who experienced virologic failure in a previous AbbVie/Abbott DAA combination study and considered an appropriate candidate for PegIFN, RBV, ABT-450/r and ABT-267 therapy. Subject must have had plasma HCV RNA level $\geq$ 2,000 IU/mL at the Pre-screening visit. Subjects who were pregnant, nursing, were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), or had any history of hepatic decompensation or evidence of hepatocellular carcinoma (HCC) were excluded.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Product	ABT-450	Ritonavir	ABT-267	RBV	PegIFN
Manufacturer	AbbVie/Abbott	AbbVie/Abbott	AbbVie/Abbott	Roche or Generic Manufacturer	Roche
Mode of Administration	Oral	Oral	Oral	Oral	SC Injection
Dosage Form	Tablet	Soft Gelatin Capsule or Tablet	Tablet	Tablet	Syringe
Strength	50 mg	100 mg	25 mg	200 mg	180 mcg/ 0.5 mL
Bulk Lot Numbers	11-000782 11-005848 12-005949	12-001426 13-002500 12-005218[a] 12-004432 13-005179 13-003954 13-004942 14-006120 14-005038	11-002034 11-002814 11-002815 14-005292	12-001630 12-007219 12-006137 12-005991 14-001215 14-005989 15-003827 12-001669	12-001215 13-003112 12-000490 12-003160 13-003830 14-002180 15-000888 15-006181

a. Lot number shipped but not used.

Duration of Treatment: 24 weeks of ABT-450 200 mg + ritonavir 100 mg + ABT-267 25 mg (all once daily) + 48 weeks of PegIFN 100 µg/week + RBV (1000 or 1200 mg divided twice daily).

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

Virologic response was assessed by HCV RNA measurement at various time-points throughout the study.

Resistance Variables:

The following resistance analyses were to be performed for subjects who experienced virologic failure: variants at each amino acid position in NS5a and NS3 were identified by population and/or clonal nucleotide sequencing (1) at baseline compared to reference sequence, and (2) at post-failure time points compared to baseline.

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-267, and RBV and serum concentrations for PegIFN were summarized.

Safety:

Safety evaluations included adverse event monitoring, vital signs, physical examination, and laboratory assessments.

Statistical Methods

Efficacy:

Analyses of primary and secondary endpoints were performed for the overall treatment cohort.

The primary efficacy endpoint was the percentage of subjects with SVR_{12} and the corresponding 95% Wilson score confidence interval were calculated.

The secondary efficacy endpoints were the percentage of subjects with SVR_{24} and the percentage of subjects with eRVR (HCV RNA < LLOQ at TI Weeks 4 through 12) both with Wilson score confidence intervals.

Resistance Analyses:

The following resistance information was analyzed for subjects who experienced virologic failure: 1) the variants at signature amino acid positions at baseline identified by population nucleotide sequencing were compared with the appropriate prototypic reference sequence, 2) the variants at available postbaseline time points identified by population or clonal nucleotide sequencing were compared with baseline and the appropriate prototypic reference sequences, 3) the persistence of viral resistance was summarized.

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, and ABT-267 were determined at each study visit up to 24 weeks. Plasma concentrations for RBV and serum concentrations for PegIFN were determined at each study visit up to 48 weeks.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. Safety data were summarized for the overall treatment cohort.

The number and percentage of subjects having DAA treatment-emergent AEs (i.e., any event that began or worsened in severity after initiation of study drug through 30 days post-DAA in Substudy 1) were tabulated by primary MedDRA System Organ Class and preferred term. The number of subjects with treatment emergent AEs also were provided with further breakdown by severity rating and relationship to DAA (ABT-450/r or ABT-267), PegIFN, and RBV. The number and percentage of subjects experiencing AEs with an onset date greater than 30 days post-DAA dosing through 30 days after the last dose of PegIFN/RBV were also tabulated by primary MedDRA System Organ Class and preferred term.

The number and percentage of subjects with post-baseline laboratory and vital sign values meeting pre specified criteria for potentially clinically significant (PCS) values during the DAA Treatment Period were summarized.

Summary/Conclusions

Efficacy Results:

SVR_{12} was achieved by 26/32 (81.3%) subjects, with a 95% CI of 64.7% to 91.1%.

Five subjects did not achieve SVR_{12} due to premature discontinuation of study drug and 1 subject relapsed by Post-treatment Week 12.

Among the MITT-GF-VF population, which excluded non-virologic failures, SVR_{12} was achieved by 26/27 (96.3%) subjects, with a 95% CI of 81.7% to 99.3%.

SVR_{24} was achieved by 25/32 (78.1%) subjects, with a 95% CI of 61.2% to 89.0%. One additional subject relapsed during the SVR_{24} window.

eRVR was achieved by 28/32 (87.5%) subjects, with a 95% CI of 71.9% to 95.0%.

Resistance Results:

Resistance analyses were conducted on the 2 GT1a-infected subjects experiencing virologic failure: 1 in the SVR_4 window and 1 in the SVR_{24} window. The subject experiencing virologic failure in the SVR_4 window did not have baseline substitutions in NS3, but had treatment-emergent Y56H plus D168A at post-treatment Week 4, which persisted through the post-treatment Week 48 time point. M28T in NS5A was detected at baseline and all post-baseline time points in this subject. The subject experiencing virologic failure in the post-treatment Week 24 time window had Q80K in NS3 and Q30R in NS5A at baseline which persisted through the post-treatment Weeks 24 or 48 time points. No treatment-emergent substitutions were seen in this subject.

Pharmacokinetic Results:

Exposures of DAAs, ritonavir, and ribavirin in the present study were generally comparable with historical data. The exposures of PegIFN were generally consistent with data reported in the PEGASYS label.

Safety Results:

The safety population included all enrolled subjects who received at least 1 dose of study drug.

The safety profile of ABT-450/r plus ABT-267, plus PegIFN/RBV for 24 weeks followed by 24 weeks of PegIFN and RBV alone was consistent with the established safety profile of PegIFN and RBV.

While the majority of subjects (90.6%) experienced treatment emergent AEs, most subjects experienced AEs with a maximum severity of mild or moderate. The 3 most frequently reported AEs were headache (43.8%), fatigue (34.4%), and nausea (28.1%). Most AEs were considered at least possibly related to PegIFN and/or RBV, while just over half were considered at least possibly related to DAAs.

One (3.1%) subject died during DAA treatment due to myocardial infarction that was considered unrelated to treatment and 1 additional subject prematurely discontinued DAAs because of AEs (anxiety and migraine). These rates are comparable to or lower than historical studies of DAAs that included PegIFN and RBV.

Treatment-emergent AEs that led to dose modification of RBV and PegIFN were common and consistent with the known side effect profile of these drugs.

Declines in total and different types of white blood cell (WBC) counts were observed throughout treatment and reversed after treatment was completed. These changes in hematology parameters are consistent with the known toxicities of PegIFN with or without RBV. No infectious complications were reported with the declines in WBC counts.

Summary/Conclusions (Continued)

Safety Results (Continued):

Hemoglobin declines were also observed throughout treatment and were consistent with RBV-induced hemolysis. Only 1 (3.1%) subject had grade 2 hemoglobin and there were no grade 3 or 4 values.

There were no grade 3 or 4 ALT, AST, or bilirubin elevations and there were no events of hepatic decompensation or hepatocellular carcinoma.

No clinically meaningful results of urinalysis, vital signs, or ECG, were observed.

Conclusions:

SVR_{12} was achieved by 81.3% of DAA-experienced subjects treated with paritaprevir/r + ombitasvir + PegIFN/RBV for 24 weeks followed by 24 weeks of PegIFN + RBV alone. One subject relapsed by Post-treatment Week 12. One additional subject relapsed during the SVR_{24} window. Safety was similar to prior studies of PegIFN + RBV alone. Given the availability of highly efficacious regimens that are both IFN- and RBV-free, this regimen is no longer relevant in today's HCV treatment landscape.