

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Not applicable		
Name of Active Ingredient: Not applicable		
Title of Study: A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection		
Coordinating Investigator: Humberto Aguilar, MD.		
Study Site(s): This was a multicenter study that was conducted in Australia, Belgium, Canada, Denmark, Germany, New Zealand, Spain, the United Kingdom (UK), and the United States (US) (including Puerto Rico). A total of 101 sites were approved to enroll subjects and 89 sites enrolled subjects.		
Publications: None		
Studied Period (Years): First Subject First Visit: 06 June 2013 Last Subject Last Visit: 20 October 2016	Phase of Development: 3	
Objectives: The objectives of this study were as follows: <ul style="list-style-type: none"> Assess the persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure (VF). Assess the durability of response for subjects who achieved 12-week sustained virologic response (SVR₁₂) with a regimen including an AbbVie DAA. Summarize results of IP-10, FibroTest, and alpha fetoprotein tests. 		
Methodology: This was a Phase 3, multicenter study to evaluate the persistence of drug resistance and the long-term durability of response in subjects who received ABT-450, ABT-333, or ABT-267 at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV. No study drug was administered during the study.		

Methodology (Continued):

Subjects were to be followed for a total of approximately 3 years after their last dose of a DAA in the previous HCV clinical study. The 3 years were to be inclusive of any post treatment period in the prior study, as well as any gaps between the end of the prior study and enrollment in this study. Subjects were required to complete the full post treatment period of the prior study before enrolling in Study M13-102. Once a subject reached 3 years post-DAA therapy, participation in this study was completed.

Limited laboratory testing was performed during the study. Only serious adverse events (SAE) that the investigator considered to be causally related to study procedures (i.e., venipunctures) were collected in this study. In addition, medical events related to liver disease/HCV infection were collected.

Number of Subjects (Planned and Analyzed):

No formal sample size calculations were performed. It was anticipated that approximately 500 subjects would participate in this study, including up to 50 subjects who experienced virologic failure (on-treatment virologic failure or post-treatment relapse through Week 48) and 450 subjects without virologic failure. A total of 478 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion:

Subjects who received at least 1 dose of ABT-450, ABT-333, or ABT-267 for the treatment of HCV in one of the following prior AbbVie Phase 2 or 3 trials were eligible to participate: Studies M11-646, M11-652, M12-746 (prior to M13-102 Amendment 2), M12-998, M13-098, M13-099, M13-386 (prior to M13-102 Amendment 2), M13-389, M13-393, M13-961, M14-002, and M14-103. Subjects received their last dose of AbbVie HCV DAA no more than 2 years prior to enrollment and completed the post-treatment period of an eligible prior study.

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

Not applicable.

Duration of Treatment:

Not applicable.

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

Not applicable.

Criteria for Evaluation

Efficacy:

The following laboratory assessments were performed: HCV RNA, FibroTest score, IP-10, and alpha-fetoprotein.

Resistance:

For subjects with detectable HCV RNA (virologic failure [VF] prior study, post-treatment relapse, or viremic in present study), resistance-associated signature amino acid variants were evaluated.

Safety:

Collection of SAEs that the investigator considered to be causally related to study procedures (i.e., venipunctures) were collected in this study. In addition, medical events related to liver disease/HCV infection were collected.

Statistical Methods

Efficacy:

The number and percentage of subjects who relapsed or had new HCV infection at any time up to the last follow-up in this study were summarized out of subjects who achieved SVR₁₂ in the previous study and enrolled in this study. The time to relapse or new infection from the end of AbbVie HCV DAA treatment for subjects who achieved HCV RNA < lower limit of quantitation (LLOQ) at the end of treatment in the previous study is displayed graphically using Kaplan-Meier curves. Similarly, the time to relapse or new infection from SVR₁₂ time point for the subset of subjects who achieved SVR₁₂ in the previous study are also displayed graphically using Kaplan-Meier curves. Data were summarized to delineate subjects with detectable HCV RNA and probable relapse ('without new infection') from subjects with detectable HCV RNA and new HCV infection ('with new infection') based on AbbVie's analysis of HCV RNA sequencing. The primary analysis was Relapse_{12overall}, defined as confirmed HCV RNA \geq LLOQ at any time after the SVR₁₂ assessment time point for a subject who achieved SVR₁₂ and had post-SVR₁₂ HCV RNA data available. Secondary analyses included Relapse₁₂ (confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR₁₂ assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment) and Relapse_{overall} (confirmed HCV RNA \geq LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the Post-treatment Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment).

Resistance:

For all subjects who experienced VF (whether before or during enrollment in Study M13-102; see definition above), a listing by subject of all baseline variants relative to prototypic reference sequence at signature amino acid positions was provided for each HCV DAA target (NS3, NS5A, and/or NS5B, as appropriate).

For all subjects who experienced VF (whether before or during enrollment in Study M13-102), the HCV-RNA amino acid sequence as determined by population or clonal sequencing at available post-baseline time points (including the previous study and Study M13-102) with an HCV RNA level of \geq 1000 IU/mL was compared to the baseline and appropriate prototypic reference amino acid sequences and tabulated for each DAA HCV target (NS3, NS5A, and/or NS5B, as appropriate). A listing by subject and time point of all post-baseline variants (by population or clonal sequencing) at signature amino acid positions relative to the appropriate prototypic reference amino acid sequences is provided.

Safety:

Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class and preferred term.

Summary/Conclusions

Efficacy Results:

A total of 457/478 (95.6%) subjects enrolled in Study M13-102 had achieved SVR₁₂ in the prior study. The median duration of follow-up (length of time since last dose of DAA in the prior study) was 153.0 weeks (range: 48 to 230). For the primary efficacy endpoint of Relapse_{12overall}, 1 subject (0.2%; N = 457) experienced relapse without new infection and 1 subject (0.2%; N = 457) experienced relapse with new infection after achieving SVR₁₂.

Summary/Conclusions (Continued)

Resistance Results:

Persistence of treatment-emergent substitutions in NS3, NS5A and NS5B was evaluated in subjects who had not achieved SVR₁₂, using analysis windows relative to the last dose of study drugs in the previous study.

Among 18 GT1a-infected subjects with post-baseline sequencing data for NS3, 11 subjects had treatment-emergent substitutions (7 subjects had D168 substitutions and 4 subjects had R155 substitutions). D168 substitutions were not detectable in any subject by PT Week 24. R155K/S were detectable in 100% (3/3) and 0% (0/3) subjects at PT Weeks 24 and 60, respectively.

Among 18 GT1a-infected subjects with post-baseline sequencing data for NS5A, 13 subjects had treatment-emergent substitutions 28 or 30. Treatment-emergent substitutions at amino acid positions 28 or 30 persisted through PT Week 60 in 90.0% (9/10) subjects, through PT Week 96 in 75.0% (6/8) subjects, and through PT Week 132 in 50.0% (4/8) subjects with available data.

Among 15 GT1a-infected subjects with post-baseline sequencing data for NS5B, 7 had treatment-emergent substitutions at signature amino acid positions. At PT Week 24, treatment emergent NS5B substitutions were detectable in 75.0% (3/4) of the GT1a-infected subjects, of which S556G was detectable in 100% (3/3) of subjects with available data. At PT Week 96, NS5B substitutions were detectable in 20.0% (1/5) of the subjects, of which S556G was detectable in 50.0% (1/2) of subjects.

Due to the small number of GT1b- and GT3a-infected subjects (n = 2 each) analyzed in this study, persistence of treatment-emergent substitutions could not be evaluated for these GTs.

Safety Results:

As study drug was not administered in this study, limited safety data were collected, which included SAEs considered related to study procedures and significant events related to liver disease and/or HCV infection.

No SAEs that the investigator considered to be causally related to study procedures were observed during the study. Four subjects had significant events related to liver disease and/or HCV infection: hepatocellular carcinoma and liver transplant (2 subjects), hepatic cirrhosis (1 subject), and concurrent events of esophageal varices hemorrhage, ascites, and hepatic encephalopathy (1 subject).

Three subjects died during the study for reasons not related to study procedures or liver disease/HCV (overdose [causative agent unknown], natural causes, and lung adenocarcinoma).

Conclusions:

Overall, these analyses indicate a durable virologic response in subjects who achieved SVR₁₂ in a previous AbbVie DAA study and low frequency of significant events related to liver disease and/or HCV infection over an observation period of up to 3 years.