# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206619Orig1s000

# MEDICAL REVIEW(S)

**NDA CLINICAL REVIEW ADDENDUM**
**NDA 206619**
**VIEKIRA PAK (ombitasvir, paritaprevir, ritonavir co-formulated tablets and dasabuvir tablets)**

Reviewer: Russell Fleischer, PA-C, MPH
Date completed: November 15, 2014

**Study M14-004: A Randomized, Open-label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (TURQUOISE-I)**

## BACKGROUND

NDA 206619 is under consideration for approval for treatment of patients with genotype 1 (GT1) hepatitis C virus (HCV) infection. In the NDA, the Applicant provided results from a number of drug-drug interaction trials supporting co-administration of VIEKIRA PAK (ABT-450/r/ABT-267 plus ABT-333) with antiretroviral agents (b) (4) these data are reviewed in more detail in the Clinical and Clinical Pharmacology reviews.

Also, at the time of NDA submission, the Applicant proposed to submit interim results from a small pilot cohort of subjects with HIV/HCV co-infection who were treated with VIEKIRA PAK for 12 or 24 weeks in an ongoing study. DAVP considered this request and agreed to review the clinical data from these subjects to determine whether they should be included in labeling during the first review cycle or whether they should be submitted at a later date when more complete data becomes available. DAVP agreed to review the data and below is a summary of the results from the pilot cohort.

In summary, the results from Part 1a of Study M14-004 suggest that treatment with the 3-DAA + RBV should provide robust anti-HCV efficacy while not negatively impacting maintenance of HIV-1 suppression, with a safety profile that is substantially similar to mono-infected subjects. (b) (4)

## REVIEW OF CLINICAL TRIAL DATA

### Objectives

The primary objectives of Study M14-004 are to assess the safety of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 and 24 weeks in HCV GT 1 infected subjects with HIV-1 co-infection and to evaluate the percentage of subjects achieving $SVR_{12}$ (HCV RNA <lower limit of quantification [LLOQ] 12 weeks following treatment) within the 12- and 24-week

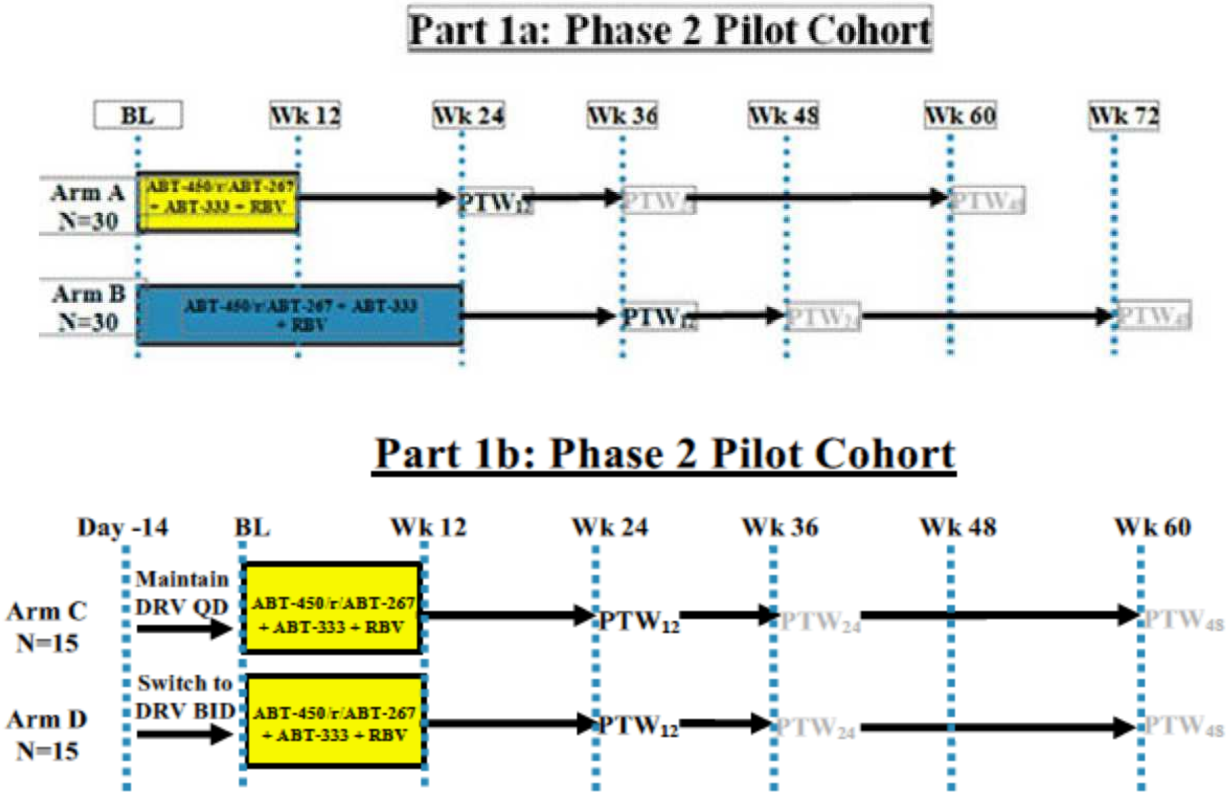
treatment groups compared to the historical SVR rate of pegIFN and RBV therapy in the corresponding population.

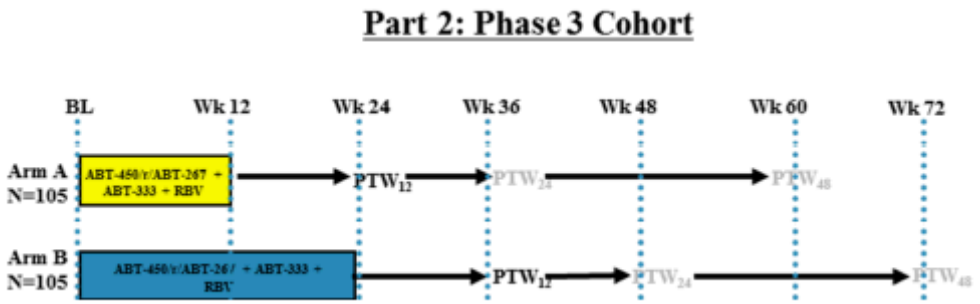
The secondary objectives are to compare the $SVR_{12}$ rates between the 12- and 24-week treatment groups and to assess the percentage of subjects with on-treatment HCV virologic failure, the percentage of subjects with HCV virologic relapse, and the percentage of subjects with plasma HIV-1 viral suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm in each treatment group.

**Investigational Plan**

Study M14-004 is a Phase 2/3, randomized, open-label, multicenter study that consists of a Phase 2 pilot cohort (Part 1a and Part 1b) and a Phase 3 cohort (Part 2).

**Figure 1. Study Schematic**






In Part 1a, subjects were randomized in a 1:1 ratio to either:

- Arm A: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV x 12 weeks
- Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV x 24 weeks

RBV was administered weight-based 1000 or 1200 mg divided twice daily with food. Subjects were stratified by prior HCV treatment history (treatment-naïve versus treatment-experienced) and by presence or absence of cirrhosis. Treatment-naïve subjects were stratified by IL28B genotype (CC versus non-CC). PegIFN/RBV-experienced subjects were stratified by type of previous response to pegIFN/RBV (null responder, partial responder, or relapse). The Part 1a cohort consisted of two HIV-1 ART regimen subgroups (atazanavir, ATV and raltegravir, RAL) each containing at least 20 subjects. Subjects are being followed for up to 48 weeks after the end of treatment.

In Part 1b, which is scheduled to begin in the fourth quarter of 2014, subjects on a stable QD darunavir (DRV)-containing HIV-1 ART regimen will be randomized to either maintain DRV QD or to switch to DRV BID administration during a pretreatment period. Beginning at Study Day 1, all subjects in Part 1b will receive ABT-450/r/ABT-267 QD + ABT-333 BID + RBV for 12 weeks during the treatment period and will be followed for 48 weeks after the end of treatment.

Part 2 of the study has not been initiated.

This interim report includes available data from Part 1a through PTW12.

**Part 1a Enrollment Criteria**

To be enrolled into Part 1a, subjects were to be: males and females between 18-70 years of age, inclusive. Subjects were to be HCV GT1/HIV-1 co-infected adults with or without compensated cirrhosis (Child-Pugh score $\leq$6). Subjects could be naïve to prior HCV treatment or have had a prior null or partial response to prior pegIFN/RBV or relapsed following pegIFN/RBV therapy. Subjects were to have unquantifiable plasma HIV-1 RNA (HIV-1 RNA <40 copies/mL) and a CD4+ T-cell count ≥200 cells/mm$^3$ or CD4+ T-cell % ≥14% while on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to screening including: two nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir plus either emtricitabine or lamivudine) plus the ritonavir-boosted protease inhibitor atazanavir, or the integrase inhibitor, raltegravir.

Of note, due to risk of transaminitis, use of estrogen-containing contraceptives was not allowed.

**Outcome Measures**

The primary outcome measure is the percentage of subjects achieving $SVR_{12}$. The main safety assessments included adverse event monitoring and vital signs, physical examination, ECG, and laboratory test assessments. Individual plasma concentrations of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, ribavirin and possible metabolites of ABT-450, ABT-267, and ABT-333 (other than ABT-333 M1) were to be tabulated and summarized.

**Study Subjects**

Subjects enrolled in Part 1a were primarily white males infected with GT1a, naïve to prior HCV treatment, and 19% had cirrhosis.

**Table 1 Part 1a demographic and disease characteristics**

| | **Arm A<br>12 Weeks<br>N=31** | **Arm B<br>24 Weeks<br>N=32** |
|---|---|---|
| Male | 29 (93.5) | 29 (91) |
| White | 24 (77) | 24 (75) |
| Mean Age | 51 ± 6.04 | 51.5 ± 8.32 |
| <55 years old | 23 (74) | 20 (62.5) |
| Prior HCV treatment status<br>-Naïve<br>-Null<br>-Partial<br>-Relapse | <br>20 (64.5)<br>5 (16)<br>5 (16)<br>1 (3) | <br>22 (69)<br>5 (16)<br>2 (6)<br>3 (9) |
| GT1a<br>GT1b | 27 (87)<br>4 (13) | 29 (91)<br>3 (9) |
| IL28B non-CC | 26 (84) | 25 (88) |
| Cirrhosis | 6 (19) | 6 (19) |
| HCV RNA ≥800,000 IU/mL | 27 (87) | 28 (87.5) |
| Mean baseline CD4 | 633.3 ± 235.57 | 625.3 ± 295.99 |
| Atazanavir | 16 (52) | 12 (37.5) |
| Raltegravir | 15 (48) | 20 (62.5) |

**Review of Efficacy**

- **HCV Outcomes**

The $SVR_{12}$ responses and reasons for non-response for all subjects in the two treatment arms are shown in Table 2 and response by prior treatment history and presence/absence of cirrhosis in GT1a-infected subjects are shown in Table 3.

**Table 2 Table $SVR_{12}$ and reasons for non-response, all subjects**

| | Arm A<br>12 Weeks<br>N=31 | Arm B<br>24 Weeks<br>N=32 |
|---|---|---|
| $SVR_{12}$ | 29 (93.5) | 29 (91) |
| On-treatment virologic failure | 0 | 1 |
| Relapse | 1 | 2 |
| Premature discontinuation | 1 | 0 |

**Table 3 $SVR_{12}$ response by treatment history and cirrhosis in subjects with GT1a**

| | **Arm A<br>12 Weeks<br>N=27** | **Arm B<br>24 Weeks<br>N=29** |
|---|---|---|
| All<br>-No cirrhosis<br>-Yes cirrhosis | 25 (92.5)<br>20/21 (95)<br>5/6 (83) | 26 (90)<br>22/24 (92)<br>4/5 (80) |
| Treatment naïve<br>-No cirrhosis<br>-Yes cirrhosis | 15/16 (94)<br>13/14 (93)<br>2/2 (100) | 19/21 (90)<br>18/20 (90)<br>1/1 (100) |
| Prior Null<br>-No cirrhosis<br>-Yes cirrhosis | 4/5 (80)<br>2/2 (100)<br>2/3 (66) | 4/5 (80)<br>1/1 (100)<br>3/4 (75) |
| Prior Partial<br>-No cirrhosis<br>-Yes cirrhosis | 5/5 (100)<br>4/4 (100)<br>1/1 (100) | 1/1 (100)<br>1/1 (100)<br>N/A |
| Prior Relapse<br>-No cirrhosis<br>-Yes cirrhosis | 1/1 (100)<br>1/1 (100)<br>N/A | 2/2 (100)<br>2/2 (100)<br>N/A |

N/A= not applicable as no subjects meeting the criteria were enrolled.

All seven of the GT1b subjects achieved an SVR, regardless of prior treatment history or presence of cirrhosis.

One subject in Arm A (GT1a, treatment-naïve, TT without cirrhosis) prematurely discontinued study medications due to withdrawn consent.

There were 4 subjects with virologic failure: 1 in Arm A and 3 in Arm B.

In Arm A, Subject 105901 was a GT1a cirrhotic who experienced relapse at PTW4. Treatment compliance by pill count was reported to be >95%; however, the 2-hour concentration values of the DAAs at the Week 4 visit were very low for this subject compared to the average values in the group of subjects who were receiving a raltegravir-containing ART regimen,

The virologic failures in Arm B were:

- Subject 119906 was a GT1a prior pegIFN/RBV null responder, TT, with compensated cirrhosis who experienced viral breakthrough during treatment on Study day 114. Resistance analysis demonstrated the V551I, Q80K, R155K, and I132I/V substitutions at time of failure.

- Subject 101907 was a 43 year old black male, GT1a treatment naïve, CT, without cirrhosis who relapsed at PTW8. This subject achieved an end-of-treatment response and appears to have been re-infected based on a phylogenetic analysis showing a different post-treatment virus compared to his pre-treatment virus. The subject reported unprotected anal intercourse with a single sexual partner throughout the Treatment and Post-Treatment periods; furthermore, the subject was aware that this reported, frequent sexual partner had chronic HCV infection. He maintained HIV RNA <40 copies/mL throughout the study period.
- Subject 101908 was a 47 year old white male, GT1a treatment naïve, CC, without cirrhosis who relapsed at PTW12. He achieved an end-of-treatment response and appears to have been re-infected based on a phylogenetic analysis showing a different post-treatment virus compared to his pre-treatment virus. Reported unprotected anal intercourse with multiple sexual partners throughout the Post-Treatment period; however, the subject was unaware of the HCV or HIV serostatus of recent sexual partners. He maintained HIV RNA <40 copies/mL throughout the study period.

***Reviewer comment: The number of subjects with cirrhosis was too small to reach conclusions about duration of treatment. In Part 1b and 2 of the study, subjects should be treated with the same duration of treatment recommended for mono-infected patients.***

- **HIV Outcomes**

At PTW12, 30/31 (97%) subjects in Arm A and 30/32 (94%) subjects in Arm B maintained HIV RNA <40 copies/mL. The one virologic failure in Arm A was the subject who prematurely discontinued from the study. A total of four subjects had HIV-1 RNA ≥40 copies/mL at the end of anti-HCV treatment or at the end of follow-up. None of the four subjects switched their ARV regimen during the study, and the two subjects with HIV-1 RNA ≥40 copies/mL (all values <200 copies/mL) at the end of anti-HCV treatment re-suppressed their HIV-1 RNA to <40 copies/mL during follow-up.

Eight other subjects had at least one study visit with HIV-1 RNA ≥40 copies/mL. Of these eight, four had transient/unconfirmed HIV-1 RNA levels ≥40 copies/mL but <200 copies/mL, three had confirmed HIV-1 RNA levels ≥40 copies/mL but <200 copies/mL, one had a confirmed HIV-1 RNA level ≥40 copies/mL with a single result ≥200 copies/mL (5,989 copies/mL), and all eight subjects had re-suppression of HIV-1 RNA to <40 copies/mL without changing their ARV regimens.

**Review of Safety**

There were no deaths, serious adverse events or discontinuations due to adverse events in the Part 1a cohort. One subject in Arm A experienced a severe tooth abscess and one in Arm B experienced severe insomnia. Two subjects in Arm B interrupted study medications due to fatigue (seven days) and increased CK level (one day).

- One subject in Arm B experienced rhabdomyolysis as a result of initiating a vigorous physical exercise program. This subject had Grade 3 AST and Grade 2 ALT elevations concurrent with an elevated total creatine kinase (15,990 U/L) at a single study visit. The subject was treated with hydration and halted his vigorous exercise program. Study treatment was not interrupted and the adverse event resolved after 6 days.

- **AIDS-Associated Opportunistic Infections**

Two subjects in Arm B experienced an AIDS-Associated opportunistic infection. Subject 112906 was diagnosed with secondary syphilis on PTD4 and was treated with intramuscular penicillin G. At the time of the event his CD4 cell count was 281 cells/$mm^3$. At the time of the submission, the event was ongoing; however, he did achieve an $SVR_{12}$. Subject 119903 was diagnosed with severe disseminated herpes zoster on treatment day 153 and was treated with gabapentin and valacyclovir. At the time of the event, his CD4 cell count was 503 cells/$mm^3$. He recovered without sequelae and achieved $SVR_{12}$.

- **General Adverse Reactions**

Treatment emergent adverse reactions occurring in ≥10% of subjects in either arm are listed in Table 4. Most events were graded as mild to moderate in severity. In co-infected subjects, fatigue occurred at a similar to higher rate, headache at a lower rate, and the other events at generally comparable rates as in mono-infected GT1-infected subjects in the primary NDA. The longer duration of treatment was associated with higher rates of insomnia, diarrhea and cough, while pruritus, fatigue and headache were reported more often by subjects treated for 12 weeks.

**Table 4 Treatment emergent adverse reactions occurring in ≥10% of any subjects**

| N (%) | Arm A N=31 | Arm B N=32 |
|---|---|---|
| Fatigue | 18 (58) | 12 (37.5) |
| Headache | 6 (19) | 4 (12.5) |
| Pruritus | 6 (19) | 2 (6) |
| Ocular icterus | 5 (16) | 1 (3) |
| Nausea | 5 (16) | 6 (19) |
| Insomnia | 5 (16) | 7 (21.5) |
| Diarrhea | 1 (3) | 4 (12.5) |
| Irritability | 3 (10) | 3 (9) |
| Cough | 2 (6.5) | 5 (16) |

- **Liver Chemistries**

The frequency of post-baseline bilirubin elevations was higher in HIV/HCV co-infected subjects compared to mono-infected subjects. As in mono-infected subjects, bilirubin levels (predominantly indirect) increased early during treatment, within 1 to 2 weeks, were generally self-limited, declined toward baseline levels by the end of treatment, and were at or near baseline levels by PTW 4. It was not possible to determine the contribution of RBV-induced hemolysis as all subjects received RBV.

**Table 5 Post-baseline bilirubin elevations**

| N (%) | Arm A N=31 | Arm B N=32 |
|---|---|---|
| Bilirubin ≥2 x ULN | 21 (68) | 13 (41) |
| Grade 2 | 12 (39) | 14 (44) |
| Grade 3 | 10 (32) | 6 (19) |
| Grade 4 | 1 (3) | 0 |

Atazanavir increases unconjugated (indirect) and total serum bilirubin that can manifest as jaundice in up to 10% of patients. These elevations are due to the inhibition of UDP glucuronyl transferase, the hepatic enzyme responsible for conjugation of bilirubin that is deficient in Gilbert's syndrome. The hyperbilirubinemia is usually mild, but can be more marked in patients with Gilbert's syndrome. The jaundice, however, is usually not indicative of hepatic injury.

Of the 17 subjects with Grade 3 or 4 bilirubin elevations, 15 were receiving atazanavir, nine also had ocular icterus, hyperbilirubinemia and jaundice. Eight subjects remained on atazanavir and one switched to raltegravir. No subjects discontinued study treatment due to an elevation in total bilirubin, which is a known effect of atazanavir.

The one subject in Arm A with a Grade 4 bilirubin level had a single value during TW2 which improved to Grade 3 upon retest.

No subjects had a post-baseline ALT >5 X ULN, and no subject met the biochemical criteria for Hy's law.

***Reviewer comment: The higher frequency of bilirubin elevations in this study may be explained by the concomitant use of atazanavir.***

- **Clinical Chemistries**

Two subjects in Arm A had low inorganic phosphate levels, and a third subject in that arm had an increased creatinine while on study medications; all three were receiving a tenofovir-containing ART regimen. For all three, these chemistry abnormalities fluctuated during the treatment period and returned to or near baseline levels by the end of the study. There were no events of renal failure and no subject had their ART regimen changed.

- **Hematology**

**Hemoglobin**

Four subjects (13%) in Arm A and three (9%) in Arm B had post-baseline hemoglobin levels <10 mg/dL; six of these subjects had a RBV dose modification due to their decreased hemoglobin levels (four in Arm A and two in Arm B). No subjects in Part 1a had a hemoglobin level <8.0 mg/dL. An additional subject in Arm A and five in Arm B had modifications to their RBV dose due to incorrect RBV dose (too low for body weight), Improvement in hemoglobin, insomnia, irritability, weight gain, fatigue, decreased weight, pruritus, and shortness of breath.

**Lymphocyte Counts**

Mean changes in absolute lymphocytes from baseline to TW12 were $-0.354 \times 10^9$/L in Arm A and $-0.345 \times 10^9$/L in Arm B. In Arm B, the mean change in absolute lymphocytes from baseline to TW24 was $-0.393 \times 10^9$/L. By PTW12, mean absolute lymphocytes increased and exceeded the mean baseline values in both treatment arms.

Overall, subjects in both treatment arms experienced mean decreases from baseline in the absolute CD4+ T-cell count during the Treatment Period without mean decreases in the absolute CD4+ T-cell percentage. By PTW12, mean absolute CD4+ T-cell counts increased and exceeded the mean baseline values in both arms.

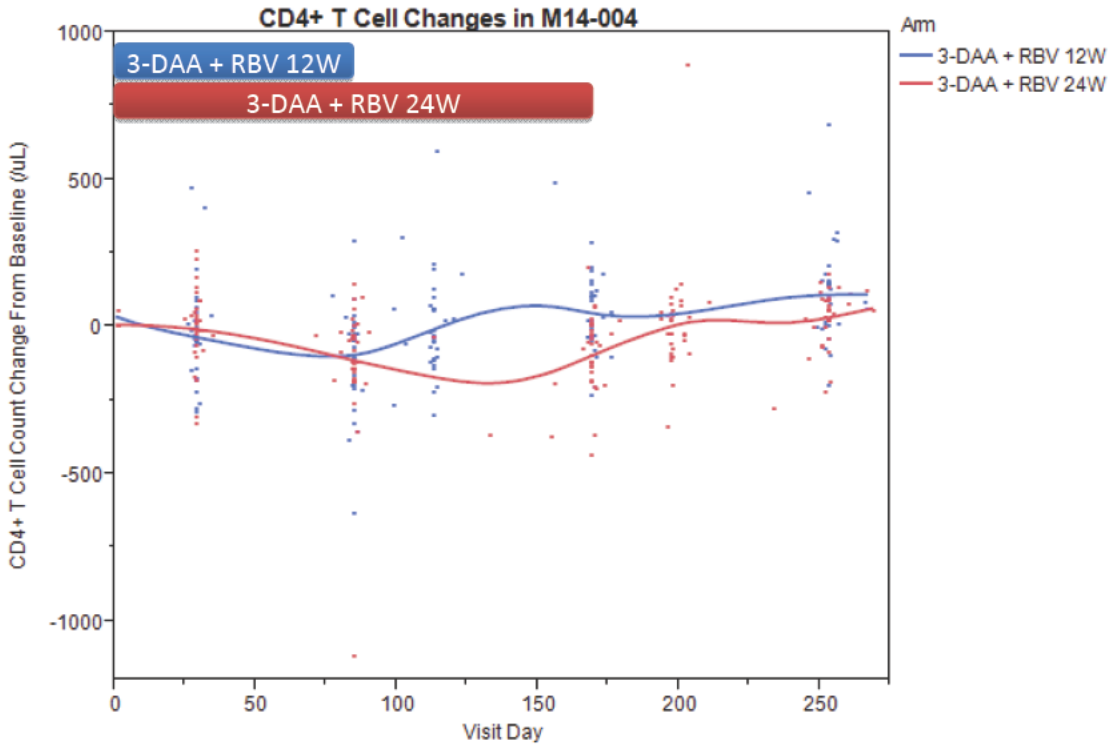
Two subjects had CD4+ T-cell levels fall to <200 cells/mm$^3$ and 1 had CD4+ percent decrease to <14% during treatment; all three were in Arm B.

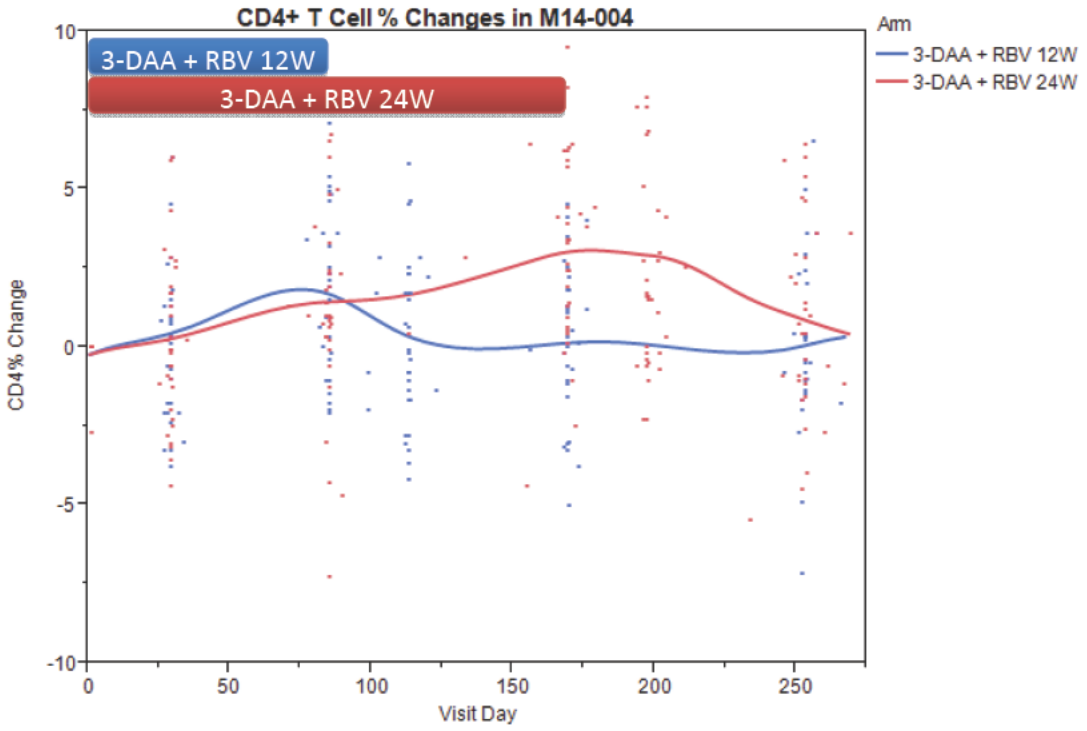
- Subject 105906 was a 52 year old treatment naïve white male, GT1a, TT, and no cirrhosis. At baseline his CD4 count was 185 cells/mm$^3$ and the CD4 percentage was 10.6%. On day 28, 230 cells/mm$^3$ and 10.8%, on day 83, 136 cells/mm$^3$ and 11.3% with complaints of cough, fatigue, anemia requiring RBV dose modifications, nausea, asymptomatic hyperbilirubinemia (predominantly indirect), and decreased short-term memory. Dapsone was started as prophylaxis; day 169 (EOT) 144 cells/mm$^3$ and 11.9%, day 202 (PTD 34) 155 cells/mm$^3$ and 13.6%, and day 251 (PTD 83), 274 cells/mm$^3$ and 11.3%. This subject achieved $SVR_{12}$ and HIV RNA <40 copies/mL.

- Subject 112901 was a 60 year old white male, GT1a, CT, treatment naïve non-cirrhotic subject. His baseline CD4 cell count was 381 cells/mm$^3$ and CD4% was 30.1%. On day 85, 152 cells/mm$^3$, 31.5% with Grade 2 total lymphocyte count of 0.61 × 10$^9$/L and grade 2 WBC of 2.9 × 10$^9$/L, and fatigue. On day 89, 137 cells/mm$^3$, 35.1% with Grade 3 lymphocyte of 0.39 × 10$^9$/L and normal WBC. On day 113, his CD4 cell count was 293 cells/mm$^3$, 33.2% and on PTD101, it was 382 cells/mm$^3$, 36.4%. This subject achieved $SVR_{12}$ and HIV RNA <40 copies/mL.

- Subject 115902 was a 69 yo white male, GT1a, CC, with no cirrhosis. At baseline his CD4 count was 256 cells/mm$^3$, and CD4% was 10.6%. During treatment he had adverse events of nausea, heartburn, dark urine, pale stools, and fatigue. On day 169 (EOT), the CD4 count was 232 cells/mm$^3$, 11.5% and at PTD 85, it was 435 cells/mm$^3$, 10.2%. The subjects achieved $SVR_{12}$ and HIV RNA <40 copies/mL.

  An analysis of changes in CD4 counts and percentages was conducted and it appears the decrease in lymphocytes were not preferential for CD4 cells (see following graphs).






***Reviewer comment: A study published in 1980 in Infection and Immunity demonstrated that ribavirin is a reversible inhibitor of lymphocyte nucleic acid synthesis and suggest that the drug may be immunosuppressive when administered in vivo. It is very difficult to find clinical data on the effects of ribavirin monotherapy on lymphocytes as almost all articles discuss the effects of the combination of interferon co-administered with RBV. Looking at the data in the primary NDA, there was a distinct, albeit small (~400 cells/mm$^3$), reduction in total lymphocyte counts in subjects treated with RBV compared to those who did not receive RBV. In the current study, all subjects received RBV so this effect may be due to an overall decrease in total lymphocyte counts, and may be due to RBV.***

***Reductions in hemoglobin levels were slightly higher than observed in mono-infected subjects, but were successfully managed with RBV dose reductions; this difference may be accentuated once more co-infected subjects are treated.***

**ASSESSMENT**

The results from the Part 1a cohort of this study suggest that treatment with the 3-DAA + RBV for either 12 or 24 weeks provided generally robust anti-HCV efficacy while not negatively impacting maintenance of HIV-1 suppression. (b) (4)

In mono-infected patients, it will be recommended that all GT1a subjects without cirrhosis be treated for 12 weeks with the 3-DAA + RBV and for 24 weeks in those with cirrhosis. For GT1b patients, the recommendation will be 3-DAA alone (no cirrhosis) and 3-DAA + RBV (cirrhosis) for 12 weeks. These regimens will be advanced into Part 2 of the study. Once the results of Part 1b become available, use of darunavir may be introduced as an alternative ART into the larger Part 2 of the study.

In general, the type and frequency of adverse reactions reported by HIV-HCV co-infected subjects were similar to those observed in the larger Phase 3 trials. The reductions in lymphocyte counts may be related to treatment with RBV.

HIV/HCV co-infected patients being treated with the 3-DAA + RBV should be monitored for reductions in CD4 cell counts and it is recommended that any patient whose CD4 cell count drops below 200 cells/mm or CD4% drops below 14%, should receive prophylaxis against opportunistic infections, and be managed according to current guidelines.

(b) (4)

**LABELING RECOMMENDATIONS**

(b) (4) Information on the outcomes of subjects with HIV-HCV co-infection will be briefly described in Section 14 and the safety information will be included in Section 6. It is recommended that until further data become available, HIV-HCV co-infected patients can be treated with the same regimens as mono-infected patients.

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RUSSELL D FLEISCHER
11/17/2014

LINDA L LEWIS
11/17/2014

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 206619 |
| Priority or Standard | Priority |
| Submit Date(s) | April 21, 2014 |
| Received Date(s) | April 21, 2104 |
| PDUFA Goal Date | December 19, 2014 |
| Division / Office | DAVP/OAP |
| Reviewer Name(s) | Russell Fleischer, PA-C, MPH |
| Review Completion Date | September 19, 2014 |
| Established Names | Ombitasvir, paritaprevir, and dasabuvir |
| Trade Name | Viekira Pak™ |
| Therapeutic Classes | NS5A inhibitor, NS3/4 protease inhibitor, and non-nucleoside NS5b-palm inhibitor |
| Applicant | AbbVie, Inc. |
| Formulations | Ombitasvir, paritaprevir and ritonavir tablets [redacted] (b) (4) dasabuvir 250 mg tablets |
| Dosing Regimen | 2 ombitasvir/paritaprevir/ritonavir co-formulated tablets once daily with food and 1 dasabuvir tablet twice daily with food with or without weight-based ribavirin for 12 or 24 weeks |
| Indications | Treatment naïve and experienced GT 1 chronic Hepatitis C virus (HCV) infected adults with and without compensated cirrhosis |
| Intended Population(s) | Adults |

Template Version: March 6, 2009

# Table of Contents

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This NDA provides preclinical and clinical data that support the approval of three new molecular entities of an NS3A protease inhibitor (ABT-450, paritaprevir) co-formulated with ritonavir + an NS5A inhibitor (ABT-267, ombitasvir) + an NS5b non-nucleoside palm inhibitor (ABT-333, dasabuvir) administered with or without ribavirin (RBV) for treatment of patients with Genotype 1 chronic hepatitis C (CHC) virus infection, including those with compensated cirrhosis and those who failed to respond to a previous course of pegylated interferon and RBV (pegIFN/RBV) therapy (3-DAA ± RBV). In all populations studied, the 3-DAA ± RBV regimen was superior to the historical efficacy rate for protease inhibitor/pegIFN/RBV therapy with a much improved safety profile. Based on a comprehensive review, this reviewer recommends that this NDA be approved. If approved, the complete regimen will be packaged and distributed under the trade-name VIEKIRA PAK™.

## 1.2 Risk Benefit Assessment

**Benefits**

The results of six Phase 3 trials conducted in GT1 CHC subjects with generally mild disease and favorable disease characteristics demonstrated very high (87% - 100%) sustained virologic response rates 12 weeks following completion of treatment ($SVR_{12}$) in all subgroups evaluated.

The clinical trials reviewed in this NDA were conducted using extensive procedures to enhance adherence and it is very likely that the SVR rates will be lower once the regimen enters general clinical practice. Efficacy data was compiled from over 2000 GT1-infected subjects evaluated in the Phase 3 program and this reviewer recommends the following dosing based on subtype, prior treatment history and presences of cirrhosis that offer the best chance of response as subjects who fail this 3-DAA regimen will have minimal retreatment options:

**GT1a treatment naïve (no cirrhosis):** The regimen of 3-DAA + RBV for 12 weeks resulted in an $SVR_{12}$ rate of 96.5% compared to 92% among subjects treated with the 3-DAA alone (no RBV). There were three treatment-naïve subjects who achieved $SVR_{12}$ who relapsed at the $SVR_{24}$ time point (all IL28B CC genotype) in the 3-DAA arm. Considering these additional virologic failures, the $SVR_{12}$ rate for the 3-DAA alone arm decreased to 88%. Therefore, the addition of RBV in this population appeared to decrease the virologic failure rate.

**GT1a treatment experienced (no cirrhosis):** The regimen of 3-DAA + RBV for 12 weeks was the only regimen evaluated in this population and it resulted in an $SVR_{12}$ rate of 96%.

**GT1b treatment naïve and experienced (no cirrhosis):** The regimen for GT 1b treatment naïve non-cirrhotic subjects should be 3-DAA alone for 12 weeks. In treatment naïve subjects, the $SVR_{12}$ rates ranged between 95-100%, and in prior pegIFN/RBV experienced subjects it was 98-100%. There was no difference in response rates between subjects who received and did not receive RBV as part of their treatment regimen.

**Compensated Cirrhosis:** Subjects with compensated cirrhosis (Childs-Pugh A) were treated for 12 or 24 weeks with the 3-DAAs + RBV. For GT1b-infected patients the recommended regimen should be 3-DAA + RBV x 12 weeks ($SVR_{12}$ 98% for 12 weeks and 100% for 24 weeks) as extending duration of treatment to 24 weeks did not provide a response advantage. Although there were small differences in the overall rates of response in GT1a subjects, it is recommended that all patients with GT1a receive 24 weeks of treatment as increasing the duration of treatment will likely provide the best chance for viral eradication in this more difficult to treat population. Specifically, increasing the duration of treatment led to an increase in $SVR_{12}$ rates from 92% to 95% in treatment naïve subjects, from 80% to 93% in prior pegIFN/RBV null responders and from 93% to 100% in subjects who relapsed after treatment with pegIFN/RBV. It is recognized that the longer duration of treatment would require additional efforts related to managing drug-drug interactions, but this risk is outweighed by the potential benefit for improved response rates. Further, with the exception of fatigue, there was no increased risk of adverse events associated with extending the duration of treatment from 12 to 24 weeks.

**Persistence of Response:** Over 98% of subjects who achieved an $SVR_{12}$ also achieved an $SVR_{24}$ in the Phase 2 and 3 trials. Of these, 99% had a persistent response and achieved $SVR_{48}$. Of note, there were 3 GT1a treatment naïve non-cirrhotic subjects treated with the 3-DAA alone who had late relapse, again supporting the need for RBV in this population. It has been shown that achievement of SVR is associated with a reduced risk of liver related morbidity and mortality. However, there were a few subjects in the compensated cirrhosis trial that achieved an SVR but had an event of esophageal varices hemorrhage suggesting that the risk of these events remains ever present.

**Post-Liver Transplantation:** Recurrence of HCV infection post liver transplantation is nearly universal. Preliminary data from a small Phase 2 trial conducted in 34 subjects treated with 3-DAA + RBV (600 mg to 800 mg) x 24 weeks with post-transplant recurrence, stable liver disease (Metavir fibrosis score $\leq$2, Child-Pugh A $\leq$6, and no evidence of hepatic decompensation) suggest that this regimen may be effective in this relatively healthy population: 97% (33/34) achieved $SVR_{12}$ (28/29 with GT1a and 5/5 with GT1b). There are significant interactions between the 3-DAA and the calcineurin inhibitors (CNIs), and a dosing plan for the CNIs was used; there were no issues with immunosuppressive therapy management. The types of adverse events were comparable to those observed in the Phase 3 trials, but the overall frequency of these events was higher, and more subjects required RBV dose modifications and erythropoietin. (b) (4)

**Opiate Substitution Therapy:** Based on clinical trial data, no reduction in efficacy or increase in toxicities is expected when the 3-DAA $\pm$ RBV are co-administered to patients receiving opiate substitution therapy (methadone, buprenorphine, and/or naloxone). Missing any data in persons who inject drugs-the group with the highest prevalence/incidence of HCV infection in the US-is disappointing.

## Risks

The safety profile of a regimen containing VIEKIRA PAK $\pm$ RBV appears manageable and has the advantages of being more tolerable compared to currently approved protease inhibitor/pegIFN/RBV-based regimens.

In over 97% of subjects, ALT levels rapidly decreased to within normal levels by treatment week four to six that persisted following completion of treatment. There is, however, a risk of transaminitis associated with the 3-DAAs, which is increased in females using systemic estrogen-containing medications. Treatment with 3-DAA ± RBV resulted in a rapid decrease from baseline in ALT levels which is consistent with reduction in viral load and hepatic inflammation caused by HCV infection. However, ~1% of 3-DAA-treated male and female subjects in the Phase 3 trials experienced post-baseline ALT elevations of ≥Grade 3; the risk was closer to 9% among females using systemic estrogen-containing products. Further, ALT elevations were observed in a healthy volunteer study evaluating estrogen-containing oral contraceptive. ALT elevations were generally asymptomatic and occurred during the first 4 weeks of study drug treatment. There were no clinical Hy's law cases based on review by an independent hepatic expert panel (most events classified as hepatocellular drug induced liver injury with adaptation). Most subjects experienced improvement or resolution by the Final Treatment Visit or by PTW 4, and, in most cases, the ALT elevation resolved with continued DAA treatment.

Based on these observations, this reviewer recommends that co-administration of estrogen-containing products be contraindicated. If prior to treatment, an estrogen-containing product is discontinued, it is likely that it can be restarted approximately 2 weeks after treatment has been completed. Discussions remain underway whether patients being treated with VIEKIRA PAK will require monitoring of liver chemistries.

Paritaprevir is a known inhibitor of the bilirubin transporter OATP1B1, which leads to asymptomatic elevations of predominantly indirect bilirubin levels. There was a statistically significant increase in mean bilirubin levels from baseline in subjects treated with 3-DAA + RBV compared to those who did not receive RBV: +1.75 mg/dL and +<1.0 mg/dL, respectively. There were no differences in the proportions of males and females with elevated bilirubin levels. Subjects treated with RBV had higher frequency of Grade 1, 2 and 3 bilirubin increases, which may have been due to hemolysis. In general, maximum bilirubin increases were observed at Week 1 (day 8), levels either stabilized or decreased during treatment, and were generally at baseline or below baseline levels by Post-Treatment Week 4

Rash and pruritus were observed in 22% and 25% of subjects treated with the 3-DAA ± RBV, respectively. Paritaprevir is an NS3/4 HCV protease inhibitor, and skin and skin structure adverse events have been reported in subjects treated with other approved protease inhibitors and RBV. In addition, RBV is associated with an increased frequency of rash and pruritus. The majority of events were graded as mild or moderate in severity and responded to treatment with topical or oral corticosteroids, oral antihistamines and/or other over-the-counter topical agents. Two subjects had a decrease in RBV dose due to pruritus, but no subject discontinued RBV or interrupted or discontinued the DAAs. There were no skin-related SAEs and no severe cutaneous reactions, such as SJS, TEN, EM or DRESS were reported.

The most important adverse event related to RBV is hemolytic anemia. The addition of RBV caused a mean 2.4 mg/dL decrease in hemoglobin levels from baseline during treatment compared to a mean 0.5 mg/dL decrease among subjects that did not receive RBV. Six percent of subjects (100/1551) treated with the 3-DAA + RBV underwent a RBV dose modification due to anemia/reduced hemoglobin, and these modifications did not negatively impact $SVR_{12}$ rates. Fatigue, abdominal pain, nausea, asthenia, insomnia, dyspnea, cough, dry skin, rash, pruritus,

and hyperbilirubinemia (due to hemolysis) occurred with higher frequency in subjects who received RBV.

Cytochrome P450 (CYP) 3A is the primary contributor to the metabolism of paritaprevir. Paritaprevir is co-formulated with a low dose of ritonavir (RTV) which is a potent inhibitor of CYP3A4 in order to increase paritaprevir's $C_{max}$ and maintain plasma half-life thereby increasing its intracellular half-life and potentiating its antiviral activity. There are a significant number of drug interactions, which will be listed as either contraindicated or to be used with caution with VIEKIRA PAK.

The 3-DAA regimen can be administered to patients with mild hepatic impairment (Childs-Pugh A, <6). Exposures of pariteprevir are increased in patients with moderate hepatic impairment (Childs-Pugh B), and the 3-DAA regimen should not be recommended for use in these patients. The 3-DAAs should be contraindicated in patients with severe liver impairment (Childs-Pugh C) as the exposures of paritaprevir increase significantly and there is risk of toxicity. The 3-DAA regimen can be administered to patients with varying degrees of renal impairment, but it is unknown if use of the 3-DAA with RBV in patients with impaired renal function will be safe; an ongoing study is evaluation this regimen.

In non-cirrhotic subjects, the data in the 3-DAA and PBO groups provide a direct comparison of natural history to active treatment and demonstrates that the 3-DAA appear to reduce the occurrence of some events and minimally increase others. It is notable that treatment with 3-DAA did not alleviate fatigue, which is one of the most common complaints among HCV-infected patients. Nausea, pruritus, diarrhea, and asthenia occurred significantly more often in among subjects treated with the 3-DAA + RBV, and all of these events have been associated with treatment with RBV.

In cirrhotic subjects, fatigue was the only adverse event reported significantly more often in the 24 week arm. Dyspnea, rash and irritability occurred with numerically greater frequency in the 24-week arm compared to the 12-week arm. Only fatigue occurred more frequently in subjects treated for 24 weeks, otherwise there were no clinically relevant differences in adverse events between cirrhotic subjects treated for 12 or 24 weeks or between cirrhotic and non-cirrhotic subjects.

Other than anemia, bilirubin elevations and transaminitis, other chemistry and hematology abnormalities occurred rarely, <2% of subjects.

There are no data, and it will be recommended that, patients who fail to respond to VIEKIRA PAK be retreated with any of the components of the regimen. Further, there are no data to support treatment of patients with VIEKIRA PAK who fail to respond to other DAA-based therapies.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A formal Risk Evaluation and Mitigation Strategy (REMS) is not required. However, because of the need for effective contraception in women receiving a RBV-containing regimen and the risk

of hepatotoxicity with or without concomitant use of estrogen-containing therapies, a Medication Guide is warranted to help mitigate the potential risk to patients receiving the 3-DAA combination.

### 1.4 Recommendations for Postmarket Requirements and Commitments

Formal discussions about PMRs and PMCs have not occurred as of the date of this review. Possible postmarketing requirements/commitments could include, but are not limited to:

- A pediatric development program
- A clinical trial in subjects with end-stage renal disease
- A clinical trial in subjects with decompensated (Child-Pugh B) hepatic impairment
- A clinical trial to determine if RBV is necessary in cirrhotic subjects with GT1b

## 2 Introduction and Regulatory Background

### 2.1 Product Information

ABT-450 (paritaprevir) is an NS3/4 protease inhibitor, ABT-267 (ombatasvir) is an NS5A inhibitor, and ABT-333 (dasabuvir) is a non-nucleoside NS5b inhibitor. Together they target and disrupt multiple stages of the hepatitis C virus (HCV) life cycle.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

HCV is a small positive-strand ribonucleic acid (RNA) virus in the Flaviviridae family (Kim, Chang, et al. 2013). At least six viral HCV genotypes have been identified, numbered 1 to 6, and most genotypes have been divided into multiple subtypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common, accounting for 70 to 80 percent of infections. The selection of treatment for chronic hepatitis C GT 1 infection depends upon factors such as prior HCV treatment history and eligibility to receive interferon.

The currently approved drugs for the treatment of GT1 HCV infection are listed in Table 1.

Pegasys® and PegIntron® are pegylated interferon alfa-2a and alfa-2b, respectively, are immunostimulatory agents and are co-administered with ribavirin. Ribavirin is a guanosine nucleoside analog. Ribavirin is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form it interferes with RNA metabolism required for viral replication. How it exactly affects viral replication is unknown; many mechanisms have been proposed for this but none of these has been proven to date. Multiple mechanisms may be responsible for its actions, but it appears to have an effect in decreasing post-treatment relapse.

Telaprevir (Incivek®), boceprevir (Victrelis®) and simeprevir (Olysio®) are NS3/4 protease inhibitors, and they disrupt specific steps in viral replication. Sofosbuvir (Solvaldi®) is a nucleoside NS5b inhibitor that also disrupts the viral life-cycle, but a different step than the protease inhibitors. All of these direct acting antiviral agents are indicated for co-administration with pegylated interferon and ribavirin.

**Table 1 Current US approved agents for treatment of GT1 infection**

| Drug Class | Generic Name | Trade Name |
|---|---|---|
| Pegylated interferons | Peginterferon alfa-2a | Pegasys® |
| | Peginterferon alfa-2b | PegIntron® |
| Interferons | Interferon alfa-2a | Roferon-A®* |
| | Interferon alfa-2b | Intron-A® |
| Nucleoside Analogue | Ribavirin | Rebetol®, Copegus® |
| Protease Inhibitors | Boceprevir | Victrelis® |
| | Telaprevir | Incivek™ |
| | Simeprevir | Olysio™ |
| NS5B Inhibitor | Sofosbuvir | Sovaldi® |

## 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients for all three DAAs are available in the US. RBV is available as both innovator and generic products.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The 3-DAA regimen proposed for marketing include an NS3/4 protease inhibitor, an NS5A inhibitor and an NS5b non-nucleoside inhibitor. There are three other NS3/4 protease inhibitors approved in the US: Olysio® (simeprevir, Janssen Pharmaceuticals), Incivek® (telaprevir, Vertex Pharmaceuticals) and Victrellis® (boceprevir, Merck and Co); all are approved for use in combination with pegIFN/RBV. Telaprevir has a Black Box Warning related to severe cutaneous adverse reactions, and it can cause anorectal symptoms, renal insufficiency/failure and anemia. Simeprevir also causes rash and photosensitivity, but not to the severity of telaprevir. Boceprevir also causes anemia. All of the protease inhibitors have significant interactions for which there are numerous drugs contraindicated for co-administration.

Adverse events associated with the approved NS5b inhibitor, sofosbuvir, include headache, and sofosbuvir does not have any significant drug-drug interactions.

There is no other NS5b non-nucleoside or NS5A inhibitors currently approved.

PegIFN is associated with considerable toxicity. Adverse side effects associated with therapy, such as severe flu-like symptoms, depression, psychoses, and anemia. The primary toxicity of ribavirin is hemolytic anemia. Other toxicities include dry skin, rash, pruritus, fatigue, and asthenia.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Individual INDs for paritaprevir, ombitasvir and dasabuvir were submitted in 2010. Initial Phase 1 studies were directed at determination of individual product safety, tolerability, pharmacokinetics and early antiviral activity. Subsequently, and based on results from

individual product studies, the three DAAs were evaluated in various combinations with and without ribavirin and/or peg-IFN. The outcomes of these early studies led to the development of a large Phase 2 study that investigated optimal doses, combinations and durations of the 3-DAA combination with and without RBV in GT1-infected patients.


An EOP2 meeting was held in October 2012. AbbVie initially proposed to conduct four studies. However, DAVP raised various concerns about these studies and recommended revisions that would streamline Phase 3 development, address specific regulatory and clinical issues. At the time of the EOP2 meeting, AbbVie stated they had already sent the protocols to study sites and IRBs and subjects were already being screened. So instead of revising the protocols, the Applicant initiated two additional studies to specifically address DAVP requests.

In April 2013, the 3-DAA regimen was granted breakthrough therapy designation based on promising clinical data from Phase 2 trials. A follow-up meeting to discuss various outstanding development issues was convened in July 2013. At the meeting, discussions took place around the format and content of various modules of the planned NDA, database development, and issues related to the multiple formulations and the impact on interpretation of drug-drug interactions and safety data.

A Pre-NDA meeting was held on January 30, 2014. Salient issues discussed included: the appropriate regimen for each GT1 subtype (1a and 1b), the duration of dosing for subjects with cirrhosis (12 versus 24 weeks), drug-drug interaction information, and safety issues.

### 2.6 Other Relevant Background Information

None

# 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission was complete, there were no quality or integrity issues, and all databases were useable.

## 3.2 Compliance with Good Clinical Practices

The Applicant attested that all clinical studies were conducted in accordance with the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and relevant regulatory requirements. Subjects were accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review boards (IRBs), ethics committee, or similar authority.

Ten investigative sites involved in the Phase 3 trials were identified and scheduled for inspection by the Division of Scientific Investigations (DSI). Eight sites were found to be in compliance with GCPs and no issues were identified that would jeopardize the integrity of the trials. The other two sites scheduled for GCP inspection were located in Israel, and due to instability in the region these inspections were cancelled.

## 3.3 Financial Disclosures

Financial disclosure documentation was reviewed. There were no instances where a single investigator had significant impact on the conduct or outcomes of the Phase 3 trials. See Appendix 9.4 for the Clinical Investigator Financial Disclosure Review.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Co-formulated ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with “AV1” on one side. Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with “AV2” on one side.

The proposed daily regimen is: 2 ombitasvir/paritaprevir/ritonavir tablets once daily with food and one dasabuvir tablet twice daily with food. The three DAAs are co-packaged as VIEKIRA PAK™ and dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons, and each weekly carton contains seven daily dose packs. VIEKIRA PAK should be stored at or below 30°C (86°F).

RBV, when necessary, is dispensed under a separate prescription.

The final outcome of quality inspections of manufacturing and testing sites are pending.

## 4.2 Clinical Microbiology

**Paritaprevir (ABT-450)** is a selective inhibitor of HCV NS3 protease. In cell culture, paritaprevir has sub- to low-nanomolar $EC_{50}$ values against HCV genotype 1a, 1b, 2a, 3a, 4a and 6a replicons. ABT-450 inhibited GT 1a and 1b replicons with $EC_{50}$ values of 0.94 and 0.32 nM in the absence of human plasma. In the presence of 40% human plasma the $EC_{50}$ increased by

24- to 27-fold. Paritaprevir has no activity against hepatitis B virus or HIV-1. Paritaprevir has ~5-fold and 19-fold reduced activity against GT2a and GT3a, respectively, compared to GT1a.

Paritaprevir demonstrates additive to synergistic activity with dasabuvir, ombitasvir, interferon-alpha and ribavirin.

In vitro resistance testing identified the following major mutations in HCV NS3: R155Q, A156T, and D168H/V/E/N; D168V conferred the highest level of reduced susceptibility (302- and 648-fold).

**Ritonavir** (RTV) is an HIV-1 protease inhibitor which in low doses is a potent inhibitor of CYP3A4. RTV is co-administered with paritaprevir to increase its exposures and maintain plasma half-life thereby increasing its intracellular half-life and potentiating its antiviral activity. RTV has no direct effect on the replication of HCV (see also Section 4.4.3).

**Dasabuvir (ABT-333)** is an inhibitor of the RNA dependent RNA polymerase encoded by the NS5B gene of HCV. The $EC_{50}$ of dasabuvir against GT 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 9 nM and 1 nM, respectively, and the activity of the M1 metabolite was 39 nM and 8 nM, respectively. The replicon activity of dasabuvir was attenuated approximately 15-fold in the presence of 40% human plasma, while the activity of the M1 metabolite was attenuated 3 to 4-fold. Dasabuvir has reduced activity against GT2, GT3 and GT4.

Dasabuvir demonstrates additive to synergistic activity with paritaprevir, ombitasvir, interferon-alpha and ribavirin.

Mutations at C316Y, M414I/T/V, E446K/Q, Y448C/H, A553T, G554S, S556G/R, and Y561H decrease susceptibility to dasabuvir.

**Ombitasvir (ABT-267)** is a NS5A inhibitor, with inhibitory concentrations in the picomolar range against GT1a and 1b in subgenomic replicon systems. In standard cell culture assays $EC_{50}$ values ranged from 5.0-14 pM. Replicon activity was attenuated by 11 to 13-fold in the presence of 40% human plasma to yield plasma adjusted $EC_{50}$ values of 190 pM for GT1a and 56 pM for genotype 1b replicons, respectively. The M23, M29, M36 and M37 metabolites were at least 78,000-fold less active than ombitasvir against the genotype 1a and 1b replicons. The $EC_{50}$ of ABT-267 against genotypes 2a, 2b, 3a, 4a, 5a and 6a ranged between 0.0003 nM and 0.075 nM.

Ombitasvir demonstrates additive to synergistic activity with paritaprevir, dasabuvir, interferon-alpha and ribavirin.

Large reductions in ombitasvir activity were conferred by a number of individual substitutions, in particular L/M28T/V, Q30R, L31F/V, and Y93C/H in GT1, F28S in GT2a, L28F and L31V in L31F in GT3a, L31V in GT5a, and L31V and T58N in GT6a. RAVs at positions 28 and 93 may persist for up to 24 weeks.

**Ribavirin** is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form it interferes with RNA metabolism required for viral replication. Its exact mechanism of action on viral replication is unknown; many mechanisms have been proposed for this but none of these

has been proven to date. Ribavirin appears to have an effect in decreasing post-treatment relapse.

## 4.3 Preclinical Pharmacology/Toxicology

**Paritaprevir**

- Adverse findings were limited to the gallbladder in mice and dogs (focal erosion and ulceration, inflammation and epithelial hypertrophy/hyperplasia)
- ABT-450 caused a 7.5-17.7% reduction in hERG tail current, but had no effect on mean arterial pressure, heart rate, systemic vascular resistance, PAP, PVR CO, LVEDP, QTc or PR interval, respiratory rate, tidal volume or minute volume
- ABT-450 was negative in an Ames mutation assay and in two in vivo genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests), but positive in an in vitro human chromosome aberration test; as such, ABT-450 has a low genotoxic risk
- ABT-450 is not carcinogenic
- In a 4- and 13-week mouse study, ABT-450/RTV caused adaptive increases in liver weights and hepatocellular hypertrophy, and increased liver enzymes; these effects were not observed in rat studies. In dogs, increased liver weights and increased alkaline phosphatase levels were observed.

**Ombitasvir**

- There were no drug-related adverse findings noted in preclinical studies
- Ombitasvir had no effect on CNS/neurobehavioral and had no effect on respiratory rate, tidal volume, or minute volume
- Ombitasvir is not clastogenic or mutagenic

**Dasabuvir**

- Adverse findings were limited to the stomach of transgenic mice (gastric hyperplasia and inflammation) at dosages ≥ 6000 mg/kg/day
- Dasabuvir is not genotoxic, mutagenic or clastogenic
- Dasabuvir demonstrated dose-related inhibition of the hERG channel and shortening of the QTc & ↑ MAP at plasma concentrations of 0.23 & 1.85 µg/ml; there was no effect on purkinge fiber
- Dasabuvir had no effects on respiratory rate, tidal volume, minute volume, or on CNS/neurobehavioral effects

**Reproductive Toxicity:** None of the DAAs demonstrated effects in reproductive parameters of male or female rats and there were no maternal or test article-related effects on survival, growth, sexual maturation, learning/memory, or reproduction in F1 generation rats. Based on these data, Viekira Pak (the 3-DAAs co-packaged together) will be labeled as Pregnancy Category B. RBV is Pregnancy Category X because it can cause significant teratogenic and/or embryocidal effects; pregnancy must be avoided during RBV treatment and up to 6-months post-treatment.

## 4.4 Clinical Pharmacology

The proposed 3-DAA regimen for marketing is: two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) co-formulated tablets administered once daily + one dasabavir (250 mg) tablets administered twice daily. The 3-DAA regimen will be administered with food.

### 4.4.1 Mechanism of Action

Paritaprevir (combined with low-dose ritonavir, ABT-450/r) is a selective inhibitor of HCV NS3 protease, ombitasvir (ABT-267) is an NS5A replication complex inhibitor and dasabuvir (ABT-333) is a selective non-nucleoside NS5B polymerase inhibitor (binds to the palm domain of the HCV polymerase). Administered together, these agents have a direct effect on multiple stages of the HCV viral life-cycle (see Section 4.2 above for additional details).

### 4.4.2 Pharmacodynamics

Individually, in subjects with GT1, there was a ~4.0 $\log_{10}$ reduction in HCV RNA from baseline following 3 days of monotherapy with ABT-450/r. The 25 mg dose of ombitasvir provided a ~3.10 $\log_{10}$ reduction from baseline in HCV RNA following three days of monotherapy. Dasabuvir doses between 25 and 100 mg per day reduced viral load by 1.4 $\log_{10}$ at steady-state with AUCs between 2.2 to 8.6 µg•hr/mL.

Following co-administration of the 3-DAAs at their proposed doses for marketing, ABT-450/r 150/100 mg QD, ombitasvir 25 mg QD and dasabuvir 250 mg BID, produced rapid reductions in HCV RNA and steady-state exposures were comparable to exposures observed when each agent was administered separately.

### 4.4.3 Pharmacokinetics

**Paritaprevir** is highly bound to plasma proteins (>97%), primarily eliminated in the bile with minimal renal elimination (<1%), with a terminal half-life of 5-8 hours. There is a supra-proportional increase (~5-fold) in exposure when co-administered with ritonavir, a ~2-fold accumulation following multiple daily dosing, with exposures ~30-300% (50-200 mg) higher in HCV-infected subjects than in healthy subjects.

Cytochrome P450 CYP3A4 is the primary contributor to the metabolism of ABT-450 and CYP3A5 to a lesser extent, and it is a substrate and inhibitor of various uptake and efflux transporters (P-gp, BCRP, OATP1B1). ABT-450's inhibition of the organic anion transporting polypeptide transporter OATP1B1 appears to contribute to clinical indirect hyperbilirubinemia. Ritonavir (RTV) is a potent inhibitor of CYP3A4 and an inhibitor of P-gp and BCRP, and increases paritaprevir exposures to maintain plasma half-life thereby increasing its intracellular half-life and potentiating its antiviral activity.

**ADME**: Paritaprevir is >97% protein bound. Unchanged parent drug was the major component of drug-related radioactivity in plasma. The majority of the administered radioactive dose (88%) was recovered in feces and only 8% was recovered in urine. In plasma, five ABT-450 metabolites were identified, including M2, M29, and trace levels of M3, M13 and M6. In urine, M13 was the major component, while in feces, M29, M2 and M3/M18 were the major

components. Unchanged ABT-450 recovered in feces and urine represented about 1% of the dose.

The exposure of ABT-450 from the co-formulated to be marketed formulation is increased 2- to 3-fold higher under non-fasting relative to fasting conditions.

**Ombitasvir**

Pharmacokinetic data show that ombitasvir:
- Is highly bound to plasma proteins (>99%)
- Primarily eliminated in the bile with minimal renal elimination (<1%)
- Has linear pharmacokinetics
- Has a terminal half-life of ~24 hours
- Has minimal accumulation after multiple dosing
- Undergoes amide hydrolysis; minor CYP3A4 contribution, and does not induce CYP1A2 or 3A4 mRNA
- Is a substrate and inhibitor of P-gp and BCRP

Administration of ombitasvir under nonfasting conditions resulted in 93% and 62% increase in $C_{max}$ and AUC values, respectively, relative to fasting conditions.

**ADME:** Ombitasvir is predominantly eliminated into the feces; 90%, with limited radioactivity (~2%) found in urine. Unchanged parent drug accounted for ~9% of total radioactivity in plasma. A total of 13 metabolites were identified in human plasma; M23, M29, M36, and M37 were present as major circulating metabolites. The $AUC_{0\text{-}192hr}$ of M29, M36, M23 and M37 were about 31%, 21%, 15%, and 14 % of the total radiochemical plasma $AUC_{0\text{-}192hr}$, respectively. Other metabolites (M5, M25, M26, and M34) accounted for < 5% of drug-related radioactivity in circulation. Minor metabolites in plasma included M25, M26, M34 and M5, which were detectable radiochemically. About 88% of the administered radioactive dose was excreted in feces and urine as ABT-267, indicating that ABT-267 was mainly eliminated as unchanged parent drug. Metabolites detected in feces were minor and included M9, M3, M2, M5, and M6 each present at less than 1% of dose.

**Dasabuvir** is highly bound to plasma proteins (>99%), primarily eliminated in the bile with minimal renal elimination (<1%), has linear pharmacokinetics, and a terminal half-life of 5-8 hours. There is a M1 metabolite which has 30-60 % activity of the parent drug. There is minimal accumulation after multiple dosing. Dasabuvir is a substrate of CYP2C8 with minor CYP3A4 contribution, and a substrate and inhibitor of P-gp and BCRP. Dasabuvir can be administered with or without food.

**Effect on each other:** The effect of each DAA on the other DAAs was evaluated.

- Effect on paritaprevir
  - dasabuvir increased paritaprevir exposure by ~50%
  - ombitasvir did not affect paritaprevir exposure
- Effect on ombitasvir
  - paritaprevir/r increased ombitasvir exposure by ~50%
  - dasabuvir did not affect ombitasvir exposure
- Effect on dasabuvir

- paritaprevir/r decreased dasabuvir exposure by ~50%
- ombitasvir increased dasabuvir exposure (~30%)

**Hepatic Impairment:** The results of a hepatic impairment study demonstrated that no dose adjustment is required in subjects with mild hepatic impairment (CTP-A <6) as changes in DAA exposures were not considered to be clinically significant. Among subjects with more advanced hepatic impairment (CPT-B and C), changes in paritaprevir and dasabuvir exposures were significantly higher: exposure of paritaprevir was 62% higher in moderate impaired subjects, and in severely impaired subjects paritaprevir and dasabuvir exposures were 920% and 320% higher, respectively, compared to subjects with normal hepatic function.

***Reviewer comment: The 3-DAA regimen will be recommended for use in subjects with mild, well-compensated hepatic impairment (Childs-Pugh A <6). A trial is planned to assess the safety and efficacy of the DAAs in subjects with moderate hepatic impairment (Childs-Pugh B), but until the data are known, the 3-DAAs will not be recommended for use in this population. The 3-DAAs should not be administered to patients with severe hepatic impairment due to substantial risks of toxicity due to significantly increased ABT-450 exposures.***

**Renal Impairment:** The results of a renal impairment study demonstrated no dose adjustment is required in subjects with mild, moderate or severe renal impairment.

**Formulation Development:** The to be marketed formulations are ombitasvir/paritaprevir/ritonavir co-formulated (b) (4) tablets each containing 75 mg of paritaprevir, 50 mg of ritonavir and 12.5 mg of ombitasvir and dasabuvir tablets containing 250 mg. Following administration of the co-formulated (b) (4) tablets with a high-fat meal, ABT-450 $C_{max}$ and AUC increased by approximately 300% and 180%; whereas, following a moderate-fat meal, $C_{max}$ and AUC increased by approximately 370% and 210%. The recommendation will be for all components of the 3-DAA regimen to be administered with food.

**Paritaprevir**

During development, multiple paritaprevir/r formulations were used. Initially a (b) (4) formulation was used in early Phase 1 and 2 trials as well as many drug-drug interaction studies. The to-be-marketed (b) (4) co-formulated tablets have ~60% higher exposure compared to the (b) (4) tablet.

Two different formulations of ombitasvir, (b) (4) tablets and (b) (4) tablets, were used in the Phase 1 and Phase 2 studies. The ABT-450/r/ombitasvir co-formulated tablets are being used in the Phase 3 studies. All of the Phase 2 studies conducted with the combination DAA regimens at the ombitasvir mg dose used the (b) (4) tablets. In addition, all of the Phase 1 DDI studies of the DAA combination regimens used either the ombitasvir (b) (4) tablets or the ABT-450/r/ombitasvir co-formulated tablets.

Pharmacokinetic results from the DDI studies conducted with paritaprevir/r tablets are qualitatively and quantitatively applicable to the paritaprevir/r/ombitasvir co-formulated tablets.

**Ombitasvir**

Ombitasvir exposures from the paritaprevir/r/ombitasvir 75/50/12.5 mg co-formulated tablets were bioequivalent to the ombitasvir 25 mg (b) (4) tablets (co-administered with paritaprevir 150 mg (b) (4) tablets and ritonavir 100 mg capsule) and comparable to the ombitasvir (b) (4) tablets co-administered with paritaprevir/r co-formulated tablets used in Phase 1 and Phase 2 studies. As such, the change in ombitasvir formulations was not expected to impact the results from the Phase 1 DDI studies.

**Dasabuvir**

Two different dasabuvir formulations, a tablet and a capsule formulation, were used in Phase 1 and Phase 2 studies, and a third formulation, an (b) (4) tablet formulation, was used in the Phase 3 studies. The tablet and capsule formulations were bioequivalent and the (b) (4) tablet formulation at 250 mg being used in the Phase 3 studies is bioequivalent to the dasabuvir tablets at the 400 mg dose used in Phases 1 and 2. The Phase 1 drug-drug interaction (DDI) studies were done with either the Phase 2 400 mg tablet or the Phase 3 250 mg tablet. Since the Phase 2 400 mg tablet is bioequivalent to the Phase 3 250 mg tablet, results of drug interaction studies were expected to be similar.

**Drug-drug Interactions:** DDI studies were conducted with various formulations and combinations of paritaprevir/r/ombitasvir with and without dasabuvir.

The Phase 3 formulation of paritaprevir/r/ombitasvir co-formulated (b) (4) tablets has ~60% higher bioavailability than earlier ABT-450 formulations in some of the DDI and clinical studies. This 60% increase in ABT-450 AUC relative to the (b) (4) formulation resulted in only up to about 20% increase in the effect of the 3-DAA regimen (evaluated by the ratio of co-administered drugs AUC with and without the DAA regimens) for the majority of studies that used the ABT-450 (b) (4) tablets.

Paritaprevir/r and dasabuvir interact with many concomitantly administered drugs, which could impact the pharmacokinetic and pharmacodynamics of the DAAs or the concomitant drugs possibly leading to a negative impact on safety and/or efficacy. CYP3A4 is the primary contributor to the metabolism of paritparevir, and it is co-formulated with a low dose of ritonavir (50 mg) which is a potent inhibitor of CYP3A4. Based on the presence of ritonavir and the results of a substantial number of DDI studies have been conducted, there is a long list of drugs for which co-administration is contraindicated or that should be used with caution (see Section 7.5.5) with this regimen. Ombitasvir does not appear to contribute to any of the drug-drug interactions observed.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

The Applicant conducted a substantial number of Phase 1 (n=17) and Phase 2 studies of the individual components and combinations of the 3-DAAs (paritparevir, ombitasvir, and dasabuvir); the studies that provided justification for the proposed regimens, doses and

durations for further evaluation in Phase 3 are described and reviewed below in Section 5.3. Table 1 provides the outline of the supportive Phase 2 and pivotal Phase 3 trials in which ~2600 GT1-infected adults were treated with the 3-DAA ± RBV for 12-24 weeks.

**Table 2 Supportive Phase 2 and Pivotal Phase 3 Trials**

| Study | Design | Population | Number of Subjects |
|---|---|---|---|
| **Phase 2** | | | |
| M11-652 (AVIATOR) | Randomized, open-label, multicenter study of 3-DAA ± RBV x 8, 12, or 24 weeks | GT1 (a and b), non-cirrhotic, treatment-naïve and null responders to previous pegIFN/RBV | N= 571 (247 received the 3-DAA ± RBV x 12-24 weeks)<br>GT 1a= 378<br>GT 1b= 190<br>(2 Other, 1 Missing) |
| M14-103 | Open-label, single-arm study of 3-DAA + RBV x 12 weeks | GT 1 (a and b), non-cirrhotic, treatment-naïve and experienced receiving methadone or buprenorphine | N= 38<br>GT 1a= 32<br>GT 1b= 6 |
| M12-999 | Open-label, single-arm study of 3-DAA + RBV x 24 weeks | GT 1 (a and b) with recurrent HCV infection post liver transplantation | N= 34 |
| **Phase 3 Placebo-controlled** | | | |
| M11-646 (SAPPHIRE-I) | Randomized, double-blind comparison of 3-DAA + RBV vs. PBO for 12 weeks | GT 1 (a and b), non-cirrhotic, treatment-naive | N= 631<br>GT 1a= 427<br>GT 1b= 204 |
| M13-098 (SAPPHIRE-II) | Randomized, open-label comparison of 3-DAA + RBV vs. PBO x 12 weeks | GT 1 (a and b), non-cirrhotic, treatment experienced | N= 394<br>GT 1a= 230<br>GT 1b= 163<br>(1 Other) |
| **Phase 3 Regimen-controlled** | | | |
| M13-099 (TURQUOISE-II) | Randomized, open-label comparison of 3-DAA + RBV x 12 or 24 weeks | GT 1 (a and b), treatment-naïve and experienced with compensated cirrhosis (Childs-Pugh A) | N= 380<br>GT 1a= 261<br>GT 1b= 119 |
| M13-389 (PEARL-II) | Randomized, open-label comparison of 3-DAA ± RBV x 12 weeks | GT 1b, non-cirrhotic, treatment-experienced | N=186 |
| M13-961 (PEARL-III) | Randomized, double-blind comparison of 3-DAA ± RBV x 12 weeks | GT 1b, non-cirrhotic, treatment-naïve | N=419 |
| M14-002 (PEARL-IV) | Randomized, double-blind comparison of 3-DAA ± RBV x 12 weeks | GT 1a, non-cirrhotic, treatment-naïve | N=305 |

*The Division agreed to accept this study report as an agreed upon late component of the NDA.

Studies M14-103 and M12-999 were conducted in parallel with the Phase 3 program, and data were not available prior to discussions of the main Phase 3 trials.

## 5.2 Review Strategy

Section 5.3 provides a summary of the early Phase 1 and Phase 2 combinations trials and descriptions of the designs of the pivotal Phase 3 trials. The clinical efficacy results from the Phase 3 trials are presented in Section 6.1 and safety results are presented in Section 7.

## 5.3 Discussion of Individual Studies/Clinical Trials

The development of the 3-DAA combination involved a substantial number of single and multiple-dose Phase 1 and 2 studies with the individual components and various combinations (PK/PD studies). Data from these studies demonstrated that after 3 days of monotherapy, in combination with each other, and/or in combination with pegIFN ± RBV, each agent achieved exposures expected to suppress HCV, produced robust antiviral efficacy, and had a generally acceptable safety profile.

The bulk of the clinical development program consists of Phase 2 Study M11-652 and the six Phase 3 trials (M11-646, M13-098, M13-389, M13-961, and M14-002) in which the safety and antiviral efficacy of various combinations and durations of treatment in GT 1-infected subgroups with and without cirrhosis were evaluated.

Study M14-103 was conducted to specifically address whether the 3-DAA + RBV could be safely co-administered with opioid substitution therapies. As an agreed upon late component, the Applicant submitted an interim report for Study M13-999, which is being conducted in subjects with recurrent HCV infection following liver transplant. Although the subjects enrolled in this trial represented a relatively healthy population of post-transplant subjects, this is a population in need of effective and safe therapies; as such, there is a reasonable basis for inclusion in this review.

**Integrated Summary of Early Phase Development**

The early development program for the 3-DAA combination consisted of 17 Phase 1 monotherapy and combination therapy trials. Findings from these trials included:

- The combination of paritaprevir/r + dasabuvir + RBV was found to not be sufficiently efficacious, especially in GT 1a-infected treatment experienced subjects, and that either an additional agent or longer duration treatment would be required.
- When ombitasvir was added to paritaprevir/r + dasabuvir ± RBV, response rates generally exceeded 90% and supported the further development of the 3-DAA regimen.
- Among the small number of subjects with virologic failure, NS3 variants D168V, R155K, and V36 emerged as the primary resistance associated variants with the R155K variants persisting to post-treatment week 48.
- The most common variants in NS5B were M414T or M414I, S556G, and C316Y. The latter variant was associated with a high degree of phenotypic resistance, but its prevalence decreased post-treatment. Variants at other positions were found to persist post-treatment including M414, S556, G554, and Y448.
- The most common variant in NS5A was the Y93H.
- A dose of dasabuvir of 800 mg BID led to more reductions in hemoglobin and hematocrit as well as total RBC counts.
- All doses of paritaprevir were associated with transient increases in predominantly indirect bilirubin levels.
- Doses of paritaprevir ≥200 mg did not increase responses in treatment naive subjects, and were associated with more adverse events of hepatic transaminitis.

Based on these findings, the Applicant initiated a single large Phase 2 trial (M11-652) that further investigated various doses, regimens, and durations of treatment in GT1A/B non-cirrhotic treatment naïve and prior null responders. This study represented a logical progression in development in order to determine the optimal doses, combinations and duration of treatment in both treatment naive and experienced subjects.

**Key Phase 2 Study**

**Study M11-652 (AVIATOR): A Randomized, Open-Label, Multicenter Study to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics, of ABT-450 with Ritonavir (ABT-450/r) in Combination with ABT-267 and/or ABT-333 With and Without Ribavirin (RBV) for 8, 12 or 24 Weeks in Treatment-Naïve and Null Responder Subjects with Genotype 1 Chronic Hepatitis C Virus Infection.**

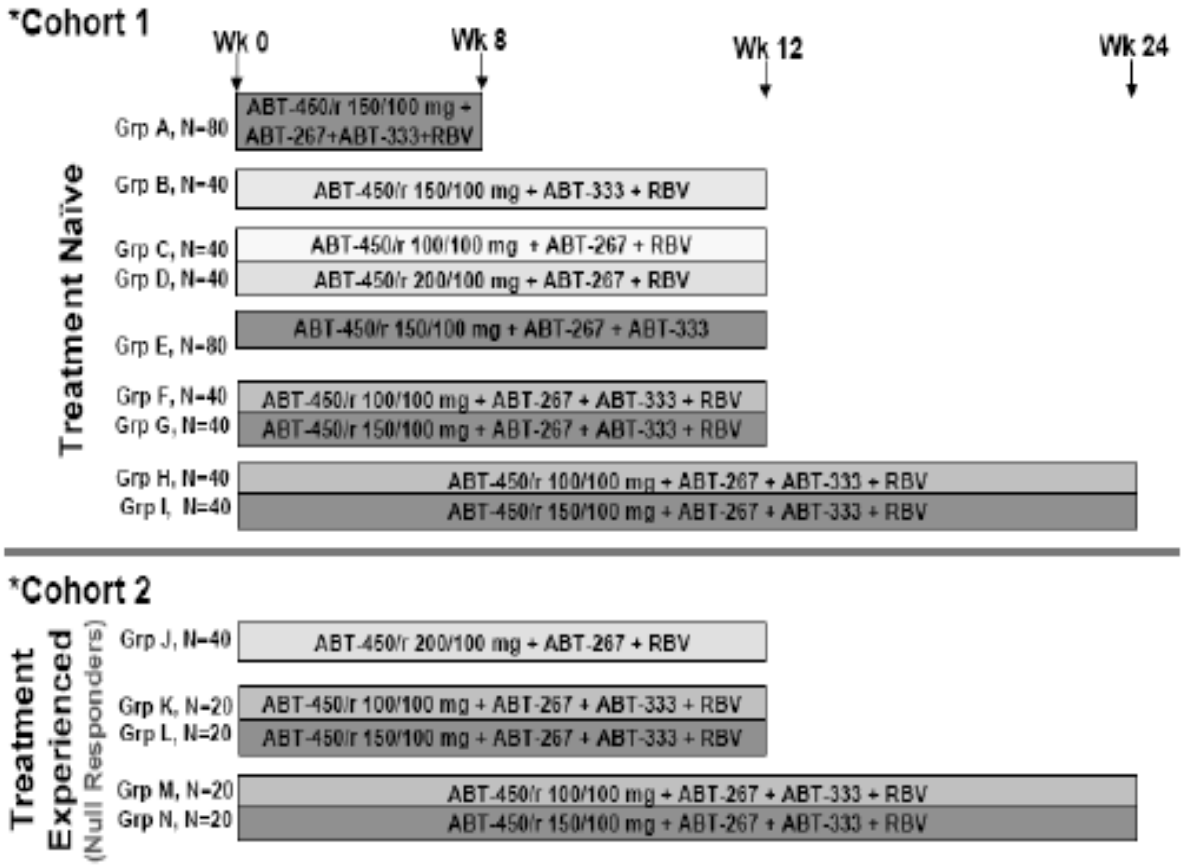
This was a Phase 2b open-label, multiple arm, multi-center study conducted between October 2011 and September 2013.

- **Objectives**

The primary objectives were to assess the safety of all treatment regimens, and to compare the percentage of subjects achieving 24-week sustained virologic response ($SVR_{24}$) following 8, 12 or 24 weeks of treatment with various combinations of the 3 DAAs ± RBV in HCV genotype 1-infected treatment-naïve subjects and prior null responders to pegIFN/RBV.

- **Investigational Plan**

Non-cirrhotic, GT 1a and 1b treatment-naïve and prior pegIFN/RBV null responders were randomized to one of 14 groups (see **Figure 1**).




Randomization within each group of treatment naïve subjects was stratified by IL28B subtype[1] (CC versus non-CC) and all subjects by HCV subtype (1a versus non-1a).

The doses used in this trial were paritaprevir/r (100/100, 150/100 or 200/100mg QD), ombitasvir 25mg QD, dasabuvir 400mg BID ± weight-based (WB) RBV (1,000 mg/day if <75 kg and 1200 mg/day if ≥75 kg).

The following criteria were considered evidence of virologic failure:

- Failure to achieve an HCV RNA decrease of at least 2 log10IU/mL at Week 1
- Confirmed increase from nadir in HCV RNA > 1 log10 IU/mL at any time point
- Failure to achieve HCV RNA < 25 IU/mL (detected or not detected) at Week 6
- Confirmed HCV RNA > LLOQ (defined as two consecutive HCV RNA measurements > LLOQ) at any point after HCV RNA < LLOQ

1 In 2009, numerous publications described a novel association between single nucleotide polymorphisms (SNPs) near the interleukin (IL) 28B gene locus and response to interferon-based treatment in subjects with CHC. Using a GWAS to investigate 300,000 to 900,000 SNPs in each sample, the investigators identified a particular SNP (rs12979860) strongly determined the outcome of interferon-based HCV therapy. Three genotypes were identified: CC, CT and TT; the CT and TT genotypes were associated with less robust virologic outcomes.

Confirmatory testing was to be completed as soon as possible, and if confirmed the subject discontinued study treatment and was offered pegIFN/RBV for up to 48 weeks, and resistance testing was to be conducted.

- **Inclusion Criteria**

Eligible subjects were to be males or females between the ages of 18 and 70 years, BMI >18 to < 38 kg/$m^2$ inclusive, with chronic infection with GT 1, HCV RNA >50,000 IU/mL, treatment naïve or prior null responder without cirrhosis (FibroTest® score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤2 at Screening, or FibroScan® result of <9.6 kPa, or the absence of cirrhosis based on a liver biopsy within the last 36 months). Screening laboratory analyses had to show the following results:

- Alanine aminotransferase (ALT) < 5 × ULN,
- Aspartate aminotransferase (AST) < 5 × ULN,
- Calculated creatinine clearance (using Cockcroft-Gault method) > 50 mL/min,
- Albumin > LLN,
- Prothrombin time INR < 1.5,
- Hemoglobin > LLN,
- Platelets > 120,000 cells per $mm^3$ for those with METAVIR score > 3 or Ishak score > 4,
- Absolute neutrophil count > 1500 cells/μL,
- Total bilirubin < 1.5 mg/dL.

- **Demographic and Disease Characteristics**

A total of 571 subjects were enrolled, randomized and treated (438 naïve and 133 prior null responders). Of the 571, 247 received treatment with 3-DAA + RBV for 12 (n=122) or 24 (n=125) weeks.

Treatment naïve subjects were males (53%) with a mean age of 50.1±10.2 years, 84% were White, 14% were Black, 8% were Hispanic, 68% had GT 1a, 72% had non-CC IL28B genotype, and the mean baseline HCV RNA was 6.53±0.55 $\log_{10}$ IU/mL.

The characteristics of the prior null responders were: male 62%, mean age 51.1±11.4 years, White 83.5%, Black 14%, Hispanic 10%, HCV GT 1a 61% , non-CC IL28B genotype 97%, and mean HCV RNA of 6.64±0.45 $\log_{10}$ IU/mL.

Twenty-nine and 50% of treatment naïve and prior null responders had ≥F2 fibrosis (no subject had cirrhosis; Ishak score ≥4), and all subjects had compensated liver disease.

There were no clinically relevant differences between dose groups or cohorts. Of note, IL28B CC subtype was lower among prior null responders compared to treatment-naive subjects (2% to 4% vs. 27% to 34%); which was expected in a pretreated population that had not responded to IFN-based therapies.

- **Subject Disposition**

Of the 571 subjects in the trial, 31 (5%) subjects prematurely discontinued study drugs and 535 (94%) subjects completed the study. The reasons for study drug discontinuation included:

adverse events (9), lost to follow-up (4), virologic failure (5), noncompliance (6) and other reasons, such as could not afford to take time off and did not want to continue study drugs (7).

- **Efficacy Outcomes**

The primary efficacy endpoint was the comparison of the percentage of treatment-naïve subjects with sustained virologic response 24 weeks ($SVR_{24}$) following 8 versus 12 weeks of treatment.

**Table 3 $SVR_{24}$ rates, Study M11-652**

| Regimen | N | Overall $SVR_{24}$ | 1a | $SVR_{24}$ | VF | Rel | 1b | $SVR_{24}$ | VF | Rel |
|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Naïve** | | | | | | | | | | |
| Group A (8 weeks) | 80 | 70 (87.5) | 56 | 47 (84) | 0 | 9 | 24 | 23 (96) | 0 | 1 |
| Group B (12 weeks) | 41 | 34 (83) | 29 | 22 (76) | 1 | 3 | 12 | 12 (100) | 0 | 0 |
| Group C (12 weeks) | 39 | 33 (85) | 26 | 20 (77) | 0 | 6 | 13 | 13 (100) | 0 | 0 |
| Group D (12 weeks) | 40 | 37 (92.5) | 26 | 23 (88.5) | 1 | 1 | 14 | 14 (100) | 0 | 0 |
| Group E (12 weeks) | 79 | 70 (89) | 52 | 45 (83) | 1 | 4 | 25 | 25 (100) | 0 | 0 |
| Group F (12 weeks) | 39 | 38 (97) | 27 | 26 (93) | 0 | 1 | 12 | 12 (100) | 0 | 0 |
| Group G (12 weeks) | 40 | 38 (95) | 27 | 25 (93) | 0 | 1 | 13 | 13 (100) | 0 | 0 |
| Group H (24 weeks) | 40 | 37 (92.5) | 27 | 25 (93) | 0 | 1[a] | 13 | 13 (100) | 0 | 0 |
| Group I (24 weeks) | 40 | 36 (90) | 27 | 23 (85) | 0 | 0 | 12 | 12 (100) | 0 | 0 |
| **Prior pegIFN/RBV Null Responders** | | | | | | | | | | |
| Group J (12 weeks) | 45 | 40 (89) | 26 | 21 (81) | 0 | 5 | 19 | 19 (100) | 0 | 0 |
| Group K (12 weeks) | 23 | 21 (91) | 15 | 13 (87) | 2 | 0 | 8 | 8 (100) | 0 | 0 |
| Group L (12 weeks) | 22 | 21 (95.5) | 13 | 12 (92) | 1 | 0 | 9 | 9 (100) | 0 | 0 |
| Group M (24 weeks) | 23 | 21 (91) | 14 | 13 (93) | 1 | 0 | 9 | 8 (89) | 0 | 0 |
| Group N (24 weeks) | 20 | 20 (100) | 13 | 13 (100) | 0 | 0 | 7 | 7 (100) | 0 | 0 |

[a] Late relapse post follow-up week 24

Evaluation of responses by IL28B genotype in GT1b-infected treatment naïve or prior null responders demonstrated no difference between those with the CC and non-CC subtypes (~100% response).

In treatment naïve GT1a subjects with the IL28B CC subtype, the overall $SVR_{24}$ rate was 89.5% (111/124) with a range from 73-100%. In subjects with the non-CC subtypes, $SVR_{24}$ rates were 90% (CT) and 88% (TT). Among treatment experienced GT1a subjects with the CC subtype, the number of subjects was extremely small (n=4) so no conclusion about efficacy in this group could be reached (this finding was expected in a population of prior IFN-based therapy failures). In subjects with non-CC subtypes, the $SVR_{24}$ rate ranged from 90% (CT) to 96% (TT).

***Reviewer comment: The variability in responses in treatment experienced GT 1a subjects with non-CC subtypes suggests that the IL28b subtype may be an important predictor of treatment outcome and warranted further assessment in Phase 3 trials.***

There were lower responses among GT1a subjects who received the 100 mg dose of ABT-450 (due to virologic failure) compared to those who received the 150 mg dose; there was no difference observed for GT1b subjects. Subjects who received the 200 mg dose of ABT-450 had higher frequencies of ALT and bilirubin elevations: 5% versus <1% and 32.5% versus 7%, respectively.

The 8-week duration of treatment was not as effective as 12 or 24 weeks in treatment naïve subjects with GT1a. Otherwise, there was no difference in response between 12 and 24 weeks of treatment in either treatment naïve or prior null responders.

A total of 55 subjects experienced virologic failure and post-baseline resistance analyses were conducted on 42 subjects. No subjects with GT1b experienced on-treatment virologic failure. The single GT1b failure was a relapse that occurred in the 8 week treatment group, and this subject had wild type virus at time of relapse.

Seven GT1a subjects (3 naïve and 4 prior null responders) had on-treatment virologic failure. Thirty subjects relapsed (25 naïve and 5 prior null responders) following completion of treatment. The most frequently detected resistance associated variants were at amino acid positions 168 (NS3), 28 and 30 (NS5A), and 556 (NS5B), which were all variants known to convey resistance to the DAAs.

Treatment arms with and without ombitasvir and dasabuvir were evaluated to determine how much each DAA added to $SVR_{24}$ rates. This analysis demonstrated that ombitasvir added +11% (-3%, +26%), and dasabuvir added +13% (-1%, +28%) to the $SVR_{24}$ among treatment naïve subjects. When comparing arms that did and did not include RBV, RBV appeared to add +7% (-5%, +18%) to $SVR_{24}$.

***Reviewer comment: At the time of the EOP2 meeting, $SVR_4$ data from all subjects and available $SVR_{12}$ data from the 8 and 12 week treatment groups were submitted, reviewed and discussed. Based on the review and discussion, the following conclusions and recommendations were made for the Phase 3 program.***

- **Genotype 1b treatment naive and experienced:** All combinations of the 3-DAAs ± RBV administered for 8, 12 or 24 weeks resulted in ~100% $SVR_{12}$ rates regardless of treatment experience or IL28B variant subtype, with only a single relapse in the 8-week treatment group. There was no additional efficacy benefit observed for 24 compared to 12 weeks of treatment in either naïve subjects or prior null responders. Based on these data, DAVP recommended the Applicant evaluate the efficacy of the 3-DAA regimen both with and without RBV in treatment naïve and experienced GT1b-infected non-cirrhotic subjects; removal of RBV from the regimen was hypothesized to lessen anemia without adversely affecting efficacy.

***Reviewer comment: The Applicant agreed to evaluate 3-DAA ± RBV in GT1b treatment naïve and pegIFN/RBV experienced subjects in a Phase 3 trial.***

- **Genotype 1a treatment naive**: Eight weeks of treatment with 3-DAAs + RBV was inadequate due to a high relapse rate (9/56, 16%). Overall, GT 1a treatment naive subjects responded well to combinations of the 3-DAAs ± RBV administered for 12 weeks with $SVR_{24}$ rates being higher when the regimen included RBV (83% versus 93%). Subjects with the CC and CT IL28B subtypes treated with the 3-DAA + RBV for 12 weeks (Groups F/G) had comparable $SVR_{24}$ rates to those who received the 3-DAA alone for 12 weeks (Group E); $SVR_{24}$ was lower for those with the TT subtype who did not receive RBV (94% versus 76%). There was no advantage to extending the duration of treatment to 24 weeks.

Based on the above data, DAVP suggested that it may be possible to remove RBV from the regimen without a substantial decrement in efficacy and recommended that a trial be designed to address this question.

***Reviewer comment: The Applicant agreed to conduct such a trial.***

- **Genotype 1a treatment experienced:** The overall response rate in GT 1a treatment-experienced subjects was 10-15% lower than in treatment-experienced subjects with GT 1b. This was likely due to the higher number of subjects with non-CC genotype. Among the GT 1a treatment-experienced non-CC subjects, the rate of virologic failure suggested that all 3 DAAs + RBV would be required to adequately treat subjects. The number of treatment-experienced subjects with the CC variant was too low to reach a conclusion (n=4); this was not unexpected as most CC genotype subjects have greater interferon sensitivity and likely had a previous favorable response to pegIFN/RBV. Again, there was no apparent advantage to extending treatment to 24 weeks.

***Reviewer comment: It was agreed that all GT1a treatment experienced subjects in the Phase 3 clinical trials should receive the 3-DAA + RBV combination for 12 weeks in order to decrease the risk of virologic failure and subsequent treatment-emergent resistance.***

- **Subjects with Cirrhosis:** There were no data on subjects with cirrhosis available at the time the Phase 3 program was initiated. It was agreed that a Phase 3 trial would be designed to compare 12 versus 24 weeks of treatment with the 3 DAAs + RBV to evaluate the potential benefit of extending treatment in this more difficult to treat population.

- **Dose Selection:** As discussed above, the ABT-450 150 mg dose was selected based on a balance between risks/benefits as doses $\geq$200 mg were associated with more frequent events of ALT and bilirubin elevations in earlier trials, and doses <150 mg were associated with lower rates of efficacy. Similarly, doses of ABT-333 >400 mg BID were associated with increased rates of reduced hemoglobin and hematocrit as well as total RBC counts. The 25 mg dose of ABT-267 consistently delivered robust antiviral activity either as monotherapy or in combination with other DAAs, with no dose-related differences in adverse events.

**Supportive Phase 2 Trials**

The Applicant provided data from two small Phase 2 trials in specific special populations: subjects on opioid substitution and subjects with recurrent HCV post-liver transplantation.

**Methadone/Buprenorphine Maintenance:** A substantial percentage of the metabolism of both methadone and buprenorphine has been attributed to CYP3A. A drug-drug interaction study between the 3 DAAs and methadone demonstrated the paritparevir $C_{max}$ and AUC values from a co-formulated (b) (4) tablet were 45-86% lower when co-administered with buprenorphine/naloxone and 50%-70% lower when co-administered with methadone. Pharmacokinetic data also demonstrated increased buprenorphine, norbuprenorphine exposures by 40-100% but no effect on naloxone exposures or opioid pharmacodynamics. Ombitasvir, ritonavir or dasabuvir exposures were not affected by methadone or buprenorphine/naloxone co-administration. These results suggested co-administration with the DAAs would not affect methadone exposures or pharmacodynamics.

At the time this interaction data became available, 24 subjects on methadone or buprenorphine/naloxone maintenance had been enrolled and treated in the Phase 2 Study M11-652 without notably poor outcomes. The Applicant suggested that the lower exposures of paritaprevir in the DDI study may have been site specific and that the timing of methadone dosing in relation to DAA dosing in Study M11-652 could not be determined with certainty, but was likely different than in the DDI study.

In Study M11-652, the 24 subjects on opiate substitution therapy were: 18 (75%) were treatment naïve and six (25%) were prior null responders. All of the subjects were GT1a. Overall, 21/24 (87.5%) achieved $SVR_{24}$; 83% (15/18) of treatment naïve and 6/6 (100%) of the prior null responders.

**Table 4 $SVR_{24}$ rates for subjects on opioid substitution therapy, Study M11-652**

| Regimen | Weeks of treatment | N | $SVR_{24}$ |
|---|---|---|---|
| **Treatment Naïve** | | | |
| ABT-450/r/267/333/RBV | 8 | 3 | 3/3 (100) |
| ABT-450/r/333/RBV | 12 | 1 | 0/1 (0) |
| ABT-450/267/RBV | 12 | 4 | 3/4 (75) |
| ABT-450/r/267/333 | 12 | 1 | 1/1 (100) |
| ABT-450/r/267/333/RBV | 12 | 5 | 5/5 (100) |
| ABT-450/r/267/333/RBV | 24 | 4 | 3/4 (75) |
| **Prior Null Responders** | | | |
| ABT-450/r/267/RBV | 12 | 1 | 1/1 (100) |
| ABT-450/r/267/333/RBV | 12 | 3 | 3/3 (100) |
| ABT-450/r/267/333/RBV | 24 | 2 | 2/2 (100) |

DAA exposure levels in subjects on methadone or buprenorphine/naloxone from M11-652 were comparable to subjects not on methadone or buprenorphine/naloxone, based on population pharmacokinetic analyses.

Despite the efficacy and pharmacokinetic findings in Study M11-652, the Applicant remained concerned that the lower paritaprevir $C_{max}$ and AUC levels could lead to lack of antiviral efficacy. In response, the Applicant excluded all subjects on methadone or buprenorphine/naloxone from the Phase 3 trials, conducted a new drug-drug interaction study, and opened a separate small Phase 2 trial to specifically investigate the safety and efficacy of a new co-formulated paritaprevir/r/ombitasvir (b) (4) tablet (63% higher AUC than the (b) (4) formulation).

The results of this new drug-drug interaction study demonstrated exposures of the DAAs in the presence of methadone or buprenorphine/naloxone were comparable to the mean exposures observed in subjects not receiving methadone or buprenorphine/naloxone in Study M11-652 and increases in exposures of buprenorphine, norbuprenorphine or naloxone were not associated with change in the pharmacodynamics.

**Study M14-103: An Open-label, Single-Arm, Phase 2 Study to Evaluate the Combination of 3-DAAs Co-administered with Ribavirin (RBV) in Adults with Genotype 1 HCV Infection taking Methadone or Buprenorphine**

- **Objectives**

The primary objectives were to assess the safety and efficacy of paritaprevir/r/ombitasvir and dasabuvir co-administered with RBV for 12 weeks in HCV GT1-infected adult subjects who were on a stable opioid replacement of methadone or buprenorphine ± naloxone.

Secondary objectives included: percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment, and to characterize the DAA pharmacokinetics in HCV-infected subjects on methadone or buprenorphine therapies.

- **Investigational Plan**

This was a Phase 2, single-arm, open-label, multi-center study. Eligible subjects were enrolled and treated with open-label paritaprevir/r/ombitasvir 150 mg/100 mg/25 mg QD, dasabuvir 250 mg BID and WB RBV for 12 weeks.

All subjects who received at least one dose of DAA in the Treatment Period and either completed treatment or prematurely discontinued study drug were monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant HCV viral variants, and assessment of PRO instruments for an additional 48 weeks following the last dose of study drug.

- **Study Subjects**

Adults between the ages of 18 and 70 years of age, inclusive, with GT1 infection who were naïve or experienced to pegIFN/RBV treatment (prior partial or null responder or prior relapser), non-cirrhotic, and on a stable opioid replacement therapy with methadone or buprenorphine ± naloxone for at least 6 months were eligible to enroll.

- **Outcome Measures**

The primary efficacy endpoint was $SVR_{12}$.

Secondary outcomes included assessment of the pharmacokinetics of paritaprevir, ritonavir, ombitasvir, dasabuvir, metabolites, RBV, S-methadone, R-methadone, buprenorphine, norbuprenorphine and naloxone.

- **Demographic and Disease Characteristics**

Thirty-eight subjects were enrolled and treated. Subjects were mostly White (95%), males (66%), <55 years of age (60%). Thirty-two (84%) had GT1a subtype, 68% had non-CC IL28B genotype, 78% had F0-F1 fibrosis, and 95% were treatment-naïve; one prior null responder and one prior relapser (both GT1a) were enrolled. Nineteen subjects were receiving methadone and 19 buprenorphine $\pm$ naloxone.

- **Disposition of Study Subjects**

Thirty-seven of 38 (97%) subjects completed study drug dosing: one subject discontinued the study due to an unrelated adverse event (sarcoma and cerebrovascular accident).

- **Efficacy Outcomes**

$SVR_{12}$ rates, by prior treatment experience, are presented in Table 5.

**Table 5 $SVR_{12}$ rates, Study M14-103**

| n/N (%) | 3-DAAs + RBV x 12 weeks N=38 |
|---|---|
| **-Overall** | 37/38 (97) |
| **-GT 1a treatment naïve** | 29/30 (97) |
| **-GT 1b treatment naive** | 6/6 (100) |
| **-GT 1a treatment experienced** | 2/2 (100) |
| **-prior null** | 1/1 (100) |
| **-prior relapse** | 1/1 (100) |
| **-GT 1b treatment experienced** | 0 |

- **Pharmacokinetic Outcomes**

- ABT-450 steady-state exposures were approximately 1.6- to 1.9-fold higher in subjects on methadone compared with subjects on buprenorphine ± naloxone.
- Steady-state exposures of ritonavir, ombitasvir, dasabuvir, dasabuvir M1, and RBV were comparable between subjects on methadone and subjects on buprenorphine ± naloxone.
- There was no difference in trough levels of DAAs, ritonavir, and RBV between subjects on methadone and subjects on buprenorphine ± naloxone.

***Reviewer comment: Based on the efficacy from 62 subjects in Study M11-652 and M14-103, and the minimal differences in DAA exposures, no detriment in efficacy is expected when the DAAs are co-administered with opioid substitution therapies, and no dose adjustments for any of the DAAs or methadone/buprenorphine/naloxone are necessary. Missing any data in persons who inject drugs-the highest prevalence/incidence group in the US-is disappointing.***

**Post Liver Transplantation**:

**Study M12-999: Open-label, Phase 2 Study to Evaluate the Safety and Efficacy of the Combination of paritaprevir/ritonavir/ombitasvir and dasabuvir with RBV in Adult Liver Transplant Recipients with Genotype 1 HCV Infection**
This ongoing Phase 2 trial enrolled 34 subjects with recurrent HCV infection post-liver transplantation that were at least 12 months post transplantation, had not received treatment for recurrent HCV infection since transplantation, had minimal hepatic impairment (Childs Pugh A), and had liver fibrosis ≤ F2 (METAVIR) on a biopsy performed within 6 months of screening (slow progressors). Subjects were assigned to treatment with paritaprevir/r/ombitasvir + dasabuvir and RBV for 24 weeks. The initial RBV dose was left to the discretion of the

investigator; 600 to 800 mg per day was the most frequently selected doses at treatment initiation. The planned duration of treatment was 24 weeks.

The results of drug-drug interaction studies with the calcineurin inhibitors (CNIs, cyclosporine and tacrolimus) used to prevent rejection indicated a large interaction between the CNIs and the 3-DAA. The protocol allowed use of CNIs at a stable dose with the following recommendations for dose adjustment:

- Tacrolimus: 500 mg once a week taken with the study drugs and with food.
- Cyclosporine: one-fifth of the pre-study total daily dose taken as a single daily dose with the study drugs and with food.

Adjustment of CNI dose and dosing interval was permitted based on the investigator's interpretation of CNI levels. Monitoring of CNI levels was scheduled regularly throughout the study with extra testing permitted at the investigator's discretion. The use of mammalian target (mTOR) inhibitors (e.g., rapamycin) was not allowed. Prednisone at a dose not exceeding 5 mg daily and mycophenolate use was permitted. Subjects were to discontinue their pre-study CNI dosing on Day –1, and initiation of the study-appropriate CNI dose was to occur on Day 1 or subsequent to Day1 based on CNI level testing and investigator preference.

- **Outcome Measures**

The primary efficacy endpoint was $SVR_{12}$.

- **Demographic and Disease Characteristics**

Thirty-four subjects were enrolled. Subjects were male (79%), White (85%), $\geq$ 55 years of age (91%), with half having a BMI ≥30 kg/$m^2$. The majority of subjects were infected with GT1a (85%, 29/34) and had an IL28B non-CC genotype (76.5%), 5 subjects were receiving cyclosporine immunosuppression, and all subjects had $\leq$F2 fibrosis. The mean time since liver transplantation was approximately 48 $\pm$ 32.53 months.

Response data from these 34 subjects demonstrated:

- 33/34 (97%) achieved $SVR_{12}$; 28/29 GT1a and 5/5 GT 1b
- One GT1a subject prematurely discontinued study drug due to possibly related adverse events of memory impairment, rash and anxiety; this subject achieved an $SVR_{12}$
- One GT1a subject relapsed on post-treatment day 3. At baseline this subject had Q80K polymorphism. At time of virologic failure, the subject had polymorphisms of R155K, Q80K, M28/T, Q30R, and G554S
- There were no issues identified with concomitant CNI administration, no episodes of rejection, and all subjects remained on their assigned CNI therapy

***Reviewer comment: Recurrence of HCV infection post liver transplantation is nearly universal and the rate of fibrosis progression can be accelerated compared to non-transplant HCV infected patients with approximately 10-25% developing cirrhosis within 5-10 years of transplantation. As such, patients with recurrent HCV following liver transplantation represent an important population with limited treatment options. The***

***preliminary results from this trial are encouraging, but it was not conducted in the population of greatest need; patients with aggressive recurrence and/or decompensated hepatic function. As such,*** (b) (4) ***the data will be included in the Special Populations section of the label. Further, the safety data suggest that liver transplant recipients experience a higher frequency of adverse events and RBV-related anemia.***

**Activity in Other Genotypes**

In vitro data demonstrated that paritaprevir has moderate nM activity against GT2 and 3 and sub- to low-nanomolar $EC_{50}$ values against GT4a. Ombitasvir has picomolar activity against GT2, 3, and 4, and dasabuvir has reduced activity against GT2, 3 and 4.

The Applicant initiated small pilot trials to evaluate subjects infected with GT2 and 3 (Studies M12-998 and M12-536) and GT4 (Study M13-393).

In **Study M12-998**, 20 GT2 and 21 GT3-infected treatment naïve non-cirrhotic subjects were randomized and treated with paritparevir/r + ombitasvir with (Arm 1) and without (Arm 2) WB RBV for 12 weeks. In Arm 1 (n=30), there were 13 females and 17 males, with a mean age of 45.2 years (range 22.0 to 64.0); 8 had GT 1a, 2 had GT 1b, 2 had GT 2a, 8 had GT 2b and 10 had GT 3a. In Arm 2 (n=31), there were 14 females and 17 males with a mean age of 49.8 years (range 27.0 to 65.0); 8 had GT 1a, 2 had GT 1b, 2 had GT 2a, 8 had GT 2b, and 11 had GT 3.

The primary endpoint was $SVR_{12}$, and the following table presents the responses for subjects infected with GT2 and GT3.

**Table 6 $SVR_{12}$ rates, GT2 and 3 subjects, Study M12-998**

| | paritaprevir/r/ombitasvir + RBV N=20 | paritaprevir/r/ombitasvir N=21 |
|---|---|---|
| **GT 2 all** | 8/10 (80) | 6/10 (60) |
| **-Subtype 2a** | 2/2 (100) | 1/2 (50) |
| **-Subtype 2b** | 6/8 (75) | 5/8 (62.5) |
| **GT 3** | 6/10 (60) | 1/11 (9) |

Four GT2b (1 + RBV, 3 - RBV) subjects experienced virologic failure: 1 breakthrough in the + RBV arm and 2 relapses and 1 breakthrough in the no RBV arm. Fourteen subjects with GT3 (4 + RBV, 10 - RBV) subjects experienced virologic failure.

**Study M12-536** enrolled 37 GT2-infected pegIFN/RBV experienced non-cirrhotic subjects (prior relapse [34] and prior partial responders [3]) and randomized them to one of two doses of paritparevir/r co-administered with ombitasvir for 12 weeks. Initially the trial was to include prior pegIFN/RBV null responders, but none were enrolled. The primary endpoint was $SVR_{12}$.

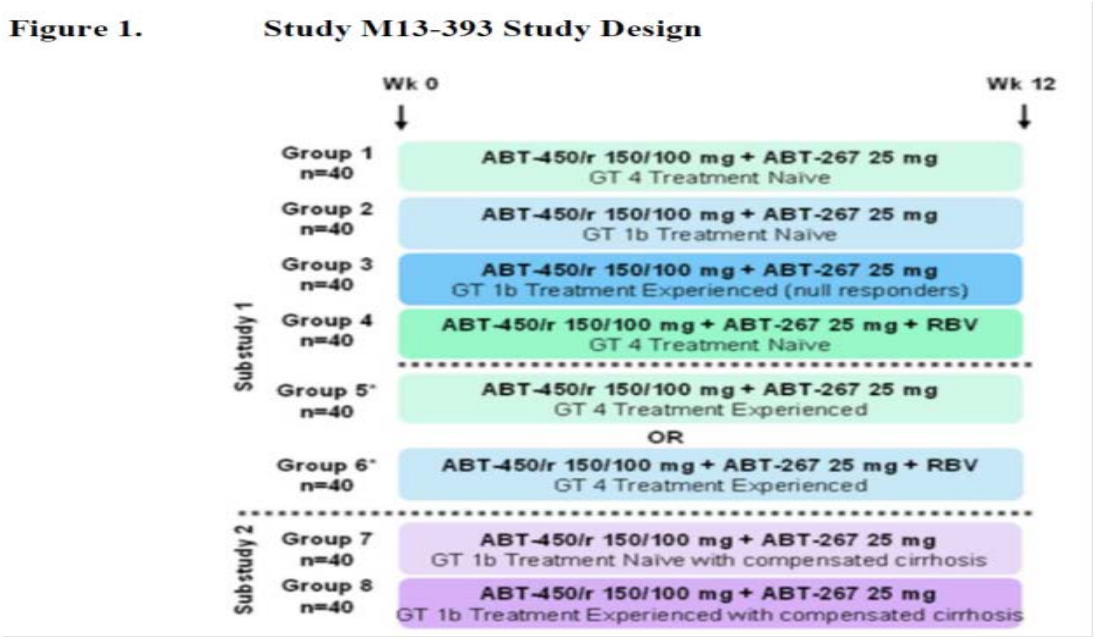
**Table 7 $SVR_{12}$ rates, Study M12-536**

| | paritaprevir/r (100/100)/ombitasvir N=19 | paritaprevir/r (150/100)/ombitasvir N=18 |
|---|---|---|
| **GT 2 all** | 11/19 (58) | 13/18 (72) |
| **-Subtype 2a** | 9/11 (82) | 3/8 (37.5) |
| **-Subtype 2b** | 2/8 (75) | 10/10 (100) |

Eight subjects in the paritaprevir/r 100/100 group experienced virologic failure: six subtype 2b (3 failures to suppress, 3 breakthroughs) and two subtype 2a (1 breakthrough and 1 relapse). In the paritparevir/r 150/100 mg group there were four subjects with virologic failure: all were subtype 2b and all had breakthrough. No subject had baseline variants. At time of virologic failure all had resistance-associated variants: D168V/Y and L28F, L31V, and/or Y93H.

**Study M13-393** was initially designed to evaluate open-label paritparevir/r + ombitasvir with and without RBV for 12 weeks in naïve and pegIFN/RBV experienced GT1b and GT4 non-cirrhotic subjects. The primary endpoint was $SVR_{12}$.

**Figure 1. Study M13-393 Study Design**




The study was subsequently modified to not enroll subjects into Group 5 (GT 4 treatment experienced to be treated with paritaprevir/r/ombitasvir without RBV) because preliminary data showed that two of 10 treatment naïve GT 4 subjects in Group 1 (paritaprevir/r/ombitasvir without RBV) experienced virologic failure: 1 breakthrough and 1 relapse.

The final three GT4 groups were:

- Group 1: Treatment naïve subjects treated with paritaprevir/r/ombitasvir x 12 weeks
- Group 4: Treatment naïve subjects treated with paritaprevir/r/ombitasvir + RBV x 12 weeks
- Group 6: Prior null responders treated with paritaprevir/r/ombitasvir + RBV x 12 weeks

All subjects had normal hepatic function and none had cirrhosis.

$SVR_{12}$ data from the three groups of GT4-infected subjects are presented in Table 7.

**Table 8 $SVR_{12}$ rates in GT4 subjects, Study M13-393**

| | paritaprevir/r/ombitasvir (Group 1) N=44 | paritaprevir/r/ombitasvir + RBV (Group 4) N-42 | paritaprevir/r/ombitasvir + RBV (Group 6) N-49 |
|---|---|---|---|
| $SVR_{12}$ | 40/44 (91) | 42/42 (100) | 49/49 (100) |
| On-treatment failure | 1 | 0 | 0 |
| Relapse | 2 | 0 | 0 |
| Premature discontinuation | 1 | 0 | 0 |

One subject (2%) in Group 1, two (5%) in Group 4, and one (2%) in Group 6 had decreases from baseline in hemoglobin levels to <10 mg/dL; no subject received erythropoietin or a blood transfusion. The most common adverse events were headache, fatigue, asthenia and nausea; the frequency of asthenia, fatigue and nausea were higher in the two groups that received RBV.

In summary:

- **Genotypes 2 and 3:** In GT2 subjects, the addition of RBV enhanced responses and decreased rates of virologic failure when co-administered with ABT-450/r/ombitasvir compared to when it was not included. Lower responses were noted in subjects with subtype 2b, which is the more prevalent subtype in the US. The overall response rates were less robust than expected and raised the question of whether the regimen of ABT-450/r/ombitasvir + RBV should continue to be developed. The response rate in GT3 subjects was modest when RBV was included and dismal when it was not part of the regimen.

***Reviewer comment:*** (b) (4)

- **Genotype 4:** Historical response rates in GT4-infected subjects treated with pegIFN/RBV have been similar to GT1-infected patients, and as such, GT4 is considered a more difficult to treat genotype. The available results of Study M13-393 suggest that GT4 treatment naïve and those previously treated with pegIFN/RBV could be treated with a regimen of ABT-450/r/ombitasvir + RBV for 12 weeks.

***Reviewer comment: Final $SVR_{12}$ data from this trial recently became available and demonstrated no decreases in efficacy from the results shown in Table 8;*** (b) (4)

## Phase 3 Pivotal Trial Designs

The Applicant conducted six Phase 3 trials, which are discussed herein. All the trials were ongoing at the time of NDA submission; however, all subjects have completed dosing and at least $SVR_{12}$ data (EOT data from the placebo groups in Studies M11-646 and M13-098) were included in the NDA; subjects remain in post-treatment follow-up. These data were sufficient to

review and to reach regulatory conclusions about the appropriate regimen for individual populations of GT1-infected adults.

In all six Phase 3 trials, the 3-DAAs were dosed as: co-formulated ombitasvir 12.5 mg/paritaprevir/r 75 mg/50 mg with two tablets taken once daily and one dasabuvir 250 mg tablet twice-daily. Ribavirin was dosed based on weight at 1000 mg for subjects ≤75 kg and 1200 mg/day for those >75 kg divided and administered twice-daily. All study drugs were to be administered with food.

- **Placebo-Controlled Trials**

The Applicant conducted two similarly designed placebo-controlled trials, one in treatment-naïve and one in prior pegIFN/RBV treated subjects.

**M11-646: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 3-DAAs Co-administered with RBV in Treatment-Naïve Adults with Genotype 1 Chronic HCV Infection (SAPPHIRE-I)**

**M13-098: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 3-DAAs Co-administered with RBV in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)**

Study M11-646 was conducted at 79 sites in the United States, Australia, Austria, Canada, France, Hungary, Italy, New Zealand, Spain, Sweden, Switzerland, and the United Kingdom. The first subject was screened on November 27, 2013 and the last subject visit for the primary analysis was on November 4, 2013; the study is ongoing with subjects in post-treatment follow-up.

Study M13-098 was conducted at 76 sites in the United States/Puerto Rico, Australia, Canada, Czech Republic, Denmark, France, Germany, Ireland, Italy, Mexico, The Netherlands, Portugal, Russia, Spain, and the United Kingdom. The first subject was screened on November 14, 2012 and the last subject's last visit for the primary analysis was December 3, 2013; the study is ongoing with subjects in post-treatment follow-up.

- **Objectives**

The primary objectives of both studies was to demonstrate the noninferiority in $SVR_{12}$ rates of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV compared to the historical SVR rate of telaprevir plus pegIFN/RBV therapy and to assess the safety of the 3-DAA combination regimen versus placebo for 12 weeks in HCV genotype 1-infected treatment naïve (M11-646) and treatment-experienced (M13-098) adults without cirrhosis.

The secondary objectives were to compare the effects of the DAAs versus PBO on normalizing ALT levels, overall $SVR_{12}$, and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment (PT) relapse.

- **Investigational Plan**

These were multicenter, randomized, double-blind, placebo (PBO) controlled trials in which HCV GT1-infected, treatment-naive or experienced adults without cirrhosis were randomized 3:1 to two treatment arms.

Arm A: Ombitasvir/paritparevir/r once daily + dasabuvir twice daily with weight-based RBV BID for 12 weeks;
Arm B: Placebos for ombitasvir/paritaprevir/r, dasabuvir and RBV for 12 weeks followed by active treatment for 12 weeks

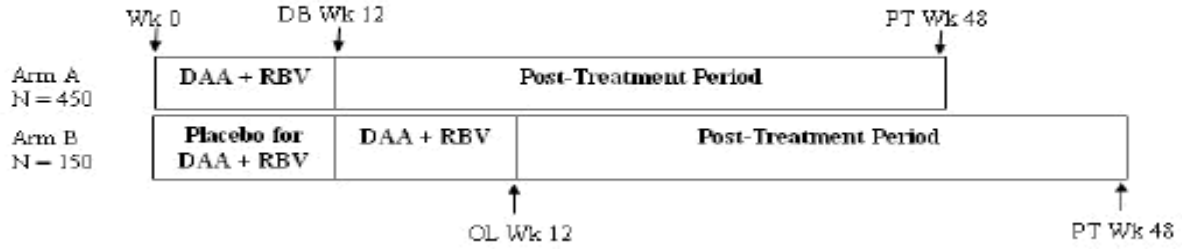
In both trials, randomization was stratified by HCV subtype (1a versus non-1a) and IL28B genotype (CC versus non-CC). In the treatment experienced trial, an additional stratification was performed by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser).

The studies consisted of three periods: The Double-Blind (DB) Treatment Period, the Open-Label (OL) Treatment Period (for subjects randomized to placebo/Arm B) and the Post-Treatment (PT) Period (for all subjects that received active study drugs).

Subjects initially randomized to PBO were offered open-label active study drugs for 12 weeks following completion of the DB Treatment Period. All subjects administered active study drugs were to be followed for 48 weeks PT to test for durability of $SVR_{12}$ and emergence or persistence of resistance.

The following cartoon provides a graphic representation of the design of the two PBO-controlled trials.

**Figure 1. Study Design**




- **Study-Specific Inclusion Criteria**

Subjects eligible to enroll in both studies were males or females between 18 and 70 years of age with GT1a or 1b CHC infection, plasma HCV RNA level >10,000 IU/mL, BMI ≥18 to <38 $kg/m^2$, and no evidence of cirrhosis, as documented by one of the following:

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score of ≥3 or an Ishak score ≤4; or
- A screening FibroTest® score of ≤0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or screening FibroScan® result of <9.6 kPa

- Subjects with a non-qualifying FibroTest/APRI or FibroScan could only be enrolled if they had a qualifying liver biopsy within 24 months prior to or during screening

In Study M11-646 subjects were to be naïve to any prior HCV treatment. In Study M13-098 subjects were to have documentation that they met one of the following prior treatment categories:

- Null-responder:
  - received at least 12 weeks of pegIFN/RBV for the treatment of HCV **and** failed to achieve a 2 $\log_{10}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
  - received less than 12 weeks of pegIFN/RBV for the treatment of HCV **and** achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at ≥Week 3.

- Partial responder:
  - received at least 20 weeks of pegIFN/RBV for the treatment of HCV and
  - achieved ≥ 2 $\log_{10}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or

- Relapser:
  - received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 24 weeks of treatment follow-up.

The number of relapsers to previous pegIFN/RBV was to be limited to ≤120 subjects, the total number of partial responders plus relapsers to previous pegIFN/RBV was to be limited to ≤300 subjects, and the number of null responders was to be limited to ~25 subjects.

- **Outcome Measures**

The primary outcome measure was the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in subjects who were randomized to and received DB active study drug. Plasma HCV RNA levels were determined for each sample using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with a lower limit of detection (LLOD) of 15 IU/mL.

The primary analysis was planned to occur after subjects who were initially randomized to active drugs completed through PTW12 or prematurely discontinued the study and subjects who were initially randomized to PBO had completed 12 weeks of OL active treatment or prematurely discontinued study drug. A follow-up analysis is to occur after subjects who received OL active treatment complete through PTW12 or prematurely discontinued the study.

In Study M11-646, to determine if the 3-DAA + RBV regimen was non-inferior or superior to the historical $SVR_{12}$ rate for the corresponding population treated with telaprevir plus pegIFN/RBV in treatment-naïve subjects, the simple percentage of subjects with $SVR_{12}$ was to be calculated with a 2-sided 95% confidence interval (CI). The lower bound of the CI was to be greater than 70% in order for the regimen to be considered non-inferior, and greater than 80% to be considered superior.

For the treatment-experienced trial (M13-098), the percentage of subjects with $SVR_{12}$ in Arm A would be considered non-inferior to the historical rate for telaprevir plus pegIFN/RBV if the lower bound of the 95% CI for $SVR_{12}$ was >60%, and for superiority >70%.

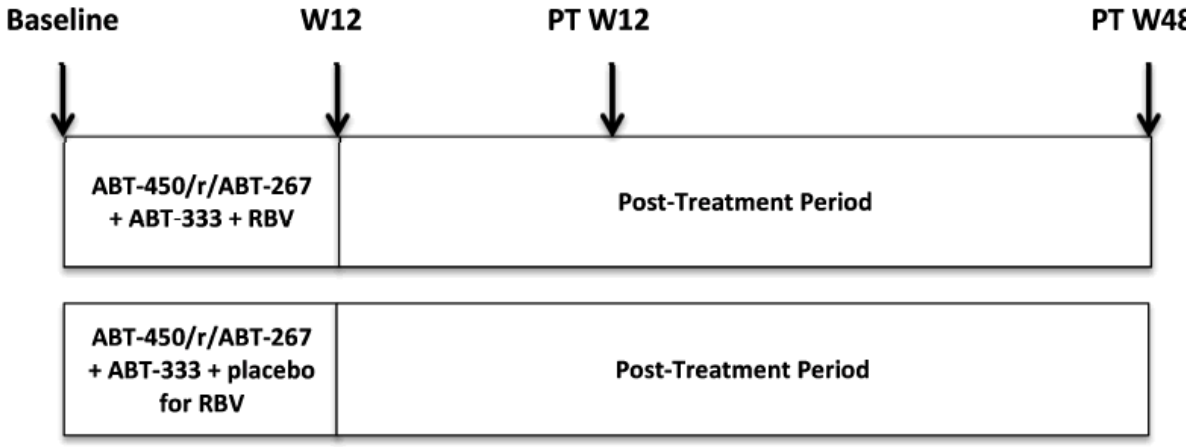
Other endpoints for evaluation included ALT normalization rate in Arm A compared to Arm B in the DB Treatment Period, the percentage of subjects in Arm A with on-treatment virologic failure during the DB Treatment Period (defined as confirmed HCV RNA ≥LLOQ after HCV RNA <LLOQ during treatment or confirmed HCV RNA ≥LLOQ at the end of treatment), and the percentage of subjects in Arm A with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA <LLOQ at the end of treatment).

- **Regimen-Controlled Trials**

In the Phase 2 trial, M11-652, it appeared that some subgroups of subjects (GT1a treatment-naïve and GT1b treatment-naïve and experienced) might achieve comparable SVR rates with or without RBV. As such, the regimen-controlled trials were specifically designed to assess the requirement for RBV in these subgroups.

Approaches to this assessment in the Phase 3 trials were a comparison of the percentage of subjects with $SVR_{12}$ and those with hemoglobin decreases during treatment between subjects treated in 3-DAA + RBV arms and the subjects treated in 3-DAA arms. The statistical analysis included a simple risk differences and accompanying 2-sided 95% confidence intervals for each study. Further, the non-inferiority in $SVR_{12}$ rates of the 3 DAA regimen to 3 DAA + RBV regimen using a –10.5% margin was assessed by calculating the difference and 2-sided 95% confidence intervals across prior treatment experience (naïve, pegIFN/RBV null responder, partial responder, or relapsers) and subgenotype using the stratum-adjusted MH proportion and its continuity corrected variance.

All of the trials used the same basic design:




Following the treatment period, all subjects administered at least one dose of study drug were to be followed for 48 weeks to monitor for safety, HCV RNA levels, and the emergence and/or

persistence of resistant viral variants. An independent DMC was empanelled for each trial to review safety data and provide recommendations to the Applicant.

**M13-389: A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450 with Ritonavir (ABT-450/r), ABT-267, and ABT-333 with and without Ribavirin in Treatment-Experienced Subjects with Genotype 1a and 1b Chronic HCV Infection (PEARL–II)**

This was a multicenter study conducted at 43 sites in the United States (US), Austria, Belgium, Italy, Portugal, Puerto Rico, Sweden, Switzerland, The Netherlands, and Turkey. The first subject was screened on August 12, 2012 and the last subject's last visit for the primary analysis was January 16, 2014; the study is ongoing with subjects in post-treatment follow-up.

- **Objectives**

The initial objectives were to evaluate the safety and efficacy of various combinations of ABT-450/r 150/100 mg plus ombitasvir 25 mg QD, plus dasabuvir 250 mg BID, with and without RBV in prior pegIFN/RBV non-responders.

Through various protocol amendments, the primary objectives evolved to an evaluation of the safety of 12 weeks of treatment with ABT-450/r/ombitasvir + dasabuvir ± RBV and to show the non-inferiority in $SVR_{12}$ rates in both arms to the historical SVR rate of telaprevir plus pegIFN and RBV therapy.

The secondary objectives were:

- to compare the percentage of subjects with a decrease in hemoglobin to below the lower limit of normal (LLN) at the end of treatment with and without RBV;
- to show the superiority in $SVR_{12}$ rates with 3-DAAs with and without RBV to the historical telaprevir plus pegIFN and RBV SVR rate;
- to show the non-inferiority in $SVR_{12}$ rates with 3-DAAs without RBV to treatment with RBV; and
- to summarize the percentage of subjects with on-treatment virologic failure and relapse.

- **Investigational Plan**

Under the initial study design, subjects were randomized to one of the following study arms:

Arm 1: 3-DAAs + RBV x 12 weeks
Arm 2: 3-DAAs x 12 weeks
Arm 3: 3-DAAs + RBV x 8 weeks
Arm 4: 3-DAAs x 8 weeks

Arms 1 and 2 were to enroll prior pegIFN/RBV null, partial responders and relapsers, and Arms 3 and 4 were to enroll only prior null responders. Randomization within each arm was to be stratified by HCV subtype (1a versus non-1a).

Prior to initiation of the trial, the protocol was amended to eliminate the 8 week duration treatment arms for subjects with HCV GT1a due to available data from Study M11-652, which demonstrated less than acceptable outcomes (see above). A second amendment excluded all subjects with HCV GT1a from the study. A third amendment modified the protocol to a Phase 3 trial, increased the sample size to up to 210 GT1b subjects, and changed randomization ratio to 1:1 for all pegIFN/RBV treatment-experienced populations (null-responders, non-responders/partial responders, and relapsers).

***Reviewer comment: The revised design addressed an interest by DAVP for a comparison of efficacy and safety outcomes for a regimen that included RBV to a regimen without RBV in treatment experienced subjects with GT1b.***

- **Study-Specific Inclusion Criteria**

To be enrolled in this trial, subjects were to be adults with CHC GT1b infection with HCV RNA >10,000 IU/mL at Screening and be prior pegIFN/RBV null responder, non-responder/partial responder, or relapsers without cirrhosis, as documented by one of the following:

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score $\leq$3 or an Ishak score of $\leq$4; or
- A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
- A screening FibroScan® result of < 9.6 kPa

Subjects with a non-qualifying FibroTest/APRI or FibroScan could only be enrolled if they had a qualifying liver biopsy within 24 months prior to or during screening.

- **Outcome Measures**

The primary outcome measure was the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm. Plasma HCV RNA levels were determined for each sample using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with a lower limit of detection (LLOD) of 15 IU/mL.

**M13-961: A Randomized, Double-blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/ritonavir/ombitasvir (ABT-450/r/ombitasvir) and dasabuvir With and Without Ribavirin (RBV) in Treatment-Naive Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL-III)**

This trial was conducted at 50 sites in in Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, Russian Federation, Spain, and the United States (US). The first subject was screened on December 11, 2012 and the last subject's last visit for primary analysis was December 12, 2013.

- **Objectives**

The primary objectives of this trial were to compare the safety of the combination of 3-DAAs with and without RBV for 12 weeks, and to show the noninferiority in $SVR_{12}$ rates (the

percentage of subjects achieving a $SVR_{12}$ of 12 weeks of treatment with 3-DAAs with and without RBV compared to the historical SVR rate of telaprevir plus pegIFN and RBV therapy in treatment-naïve CHC GT 1b-infected adults without cirrhosis.

- **Investigational Plan**

This was a randomized, double-blind, controlled, multicenter study that evaluated the combination of 3-DAAs with and without RBV. Treatment-naïve, GT1b-infected adults without cirrhosis randomized to 3-DAAs + RBV or 3-DAA alone and treated for 12 weeks. Subjects were stratified by IL28B genotype (CC versus non-CC).

The duration of the study was up to 60 weeks consisting of two periods: the Treatment Period and the Post-Treatment Period. In the Treatment Period subjects received 12 weeks of therapy. In the Post-Treatment Period, all subjects administered at least one dose of study drug were to be followed for 48 weeks.

- **Study-Specific Inclusion Criteria**

Subjects eligible to enroll in both studies were males or females between 18 and 70 years of age with GT1b CHC infection, plasma HCV RNA level >10,000 IU/mL, BMI $\geq$18 to <38 $kg/m^2$, and absence of cirrhosis, as documented by one of the following:

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score of 3 or less or an Ishak score of 4 or less; or
- A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
- A screening FibroScan® result of < 9.6 kPa
- Subjects with a non-qualifying FibroTest®/APRI or FibroScan could only be enrolled if they had a qualifying liver biopsy within 24 months prior to or during screening

- **Outcome Measures**

The primary outcome measure was the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm. Plasma HCV RNA levels were determined for each sample using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with a lower limit of detection (LLOD) of 15 IU/mL.

The primary efficacy endpoints were: $SVR_{12}$: noninferiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound of 2-sided 95% confidence interval for the percentage of subjects with $SVR_{12}$ in Arm B must exceed 73% to achieve noninferiority, and $SVR_{12}$: noninferiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB for the percentage of subjects with $SVR_{12}$ in Arm A must exceed 73% to achieve noninferiority.

Secondary efficacy endpoints include: $SVR_{12}$: noninferiority of Arm B to Arm A, using a noninferiority margin of 10.5%, comparison of the percentage of subjects with a decrease in hemoglobin to below the lower limit of normal (LLN) while on treatment for Arm A versus Arm B, $SVR_{12}$: superiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV

therapy – LCB must exceed 84% to achieve superiority, and $SVR_{12}$: Superiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB must exceed 84% to achieve superiority.

The primary analysis occurred after all enrolled subjects completed the Post-Treatment Week 12 Visit or prematurely discontinued the study.

**M14-002: A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection (PEARL-IV)**

- **Investigational Plan**

This was a Phase 3, multicenter, randomized, double-blind, placebo controlled study conducted at 53 investigative sites in the United States, Canada and the United Kingdom beginning March 14, 2013 with the last subject visit for the primary analysis taking place on December 12, 2013.

Approximately 300 HCV GT-1a-infected, treatment-naive adults without cirrhosis were to be randomized to 3-DAA + RBV or 3-DAA alone in a 1:2 ratio and treated for 12 weeks. The rationale for this trial was to determine if treated with the 3 DAAs would be sufficient. Subjects were stratified by IL28B genotype (CC versus non-CC).

- **Study-Specific Inclusion Criteria**

Subjects eligible to enroll were males or females between 18 and 70 years of age with GT 1a CHC infection who were naïve to prior treatment, plasma HCV RNA level >10,000 IU/mL, BMI $\geq$18 to <38 $kg/m^2$, and absence of cirrhosis, as documented by one of the following:

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score of 3 or less or an Ishak score of 4 or less; or
- A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
- A screening FibroScan® result of < 9.6 kPa
- Subjects with a non-qualifying FibroTest®/APRI or FibroScan could only be enrolled if they had a qualifying liver biopsy within 24 months prior to or during screening

- **Outcome Measures**

The primary outcome measure was the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm. Plasma HCV RNA levels were determined for each sample using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with a lower limit of detection (LLOD) of 15 IU/mL.

The primary efficacy endpoints were: $SVR_{12}$: noninferiority of Arms A and B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound of 2-sided 95% CI for the percentage of subjects with $SVR_{12}$ must exceed 65% to achieve noninferiority.

Secondary efficacy endpoints included:

- Comparison of the percentage of subjects with a decrease in hemoglobin at the end of treatment
- Superiority of 3-DAA + RBV treatment arm to the historical rate for telaprevir/pegIFN/RBV - LCB must exceed 75%;
- Superiority of the 3-DAA arm to the historical rate for telaprevir/pegIFN/RBV – LCB must exceed 75%
- Non-inferiority of 3-DAAs to 3-DAA + RBV using a non-inferiority margin of 10.5%.

Other secondary endpoints were the percentage of subjects with virologic failure and relapse.

- **Compensated Cirrhosis Trial**

**M13-099: A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of 3-DAAs Co-administered with RBV in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)**

- **Objectives**

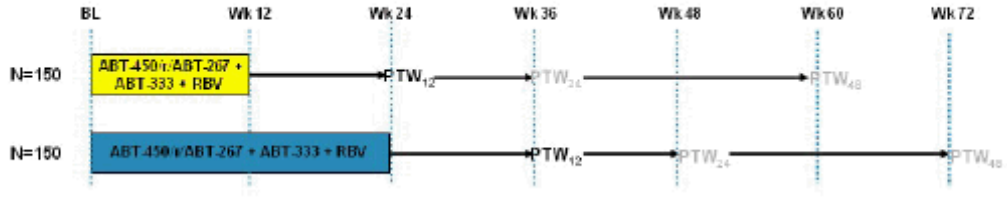
The primary objectives were to assess the efficacy and safety of the regimen 3-DAAs + RBV for 12 or 24 weeks in treatment naïve and pegIFN/RBV experienced subjects with compensated cirrhosis.

- **Investigational Plan**

This was a randomized, open-label, multicenter trial conducted at 75 sites around the world. The first subject was screened on October 24, 2012 and the last subject's last visit for primary analysis was January 24, 2014.

Eligible subjects were randomized to 12 or 24 weeks of treatment until approximately 300 subjects had been enrolled. The first 200 subjects were randomized 3:5 to the 12- and 24 week arms. After the first 200 subjects were enrolled, 100 additional subjects were then randomized 3:1 to the 12- and 24-week arms. The study schematic is shown below.

**Figure 1. Study Schematic**




Subjects were first stratified by previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. No more than 180 treatment-naïve subjects were to enroll. The treatment-naïve subjects were stratified by HCV subgenotype (1a versus non-1a) and by IL28B

genotype (CC versus non-CC). The treatment-experienced subjects were stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapsers) and by HCV subgenotype (1a versus non-1a).

- **Study-Specific Inclusion Criteria**

Subjects eligible to enroll were males or females between 18 and 70 years of age with genotype 1 chronic HCV-infection, compensated cirrhosis defined as a Child-Pugh Score of ≤ 6, and plasma HCV RNA level > 10,000 IU/mL. Documentation of cirrhosis was by one of the following methods:

- Histologic diagnosis on liver biopsy performed within 36 months of Screening or during the Screening Period, e.g., Metavir Score of > 3 (including 3/4),
- Ishak score of > 4 or,
- FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

Subjects were to have never received antiviral treatment (including pegIFN/RBV) or have documentation that they meet one of the following categories (treatment-experienced subject):

- Null-responder:
  - received at least 12 weeks of pegIFN/RBV for the treatment of HCV **and** failed to achieve a 2 log10 reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
  - received less than 12 weeks of pegIFN/RBV for the treatment of HCV **and** achieved a < 1 log10 IU/mL reduction in HCV RNA at ≥Week 3.

- Partial responder:
  - received at least 20 weeks of pegIFN/RBV for the treatment of HCV and
  - achieved ≥ 2 log10 reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or

- Relapser:
  - received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 24 weeks of treatment follow-up.

Treatment experienced subjects must have received their last dose of prior pegIFN/RBV therapy administered >2 months prior to Screening.

- **Outcome Measures**

The primary outcome measure was the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm. Plasma HCV RNA levels were determined using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with a lower limit of detection (LLOD) of 15 IU/mL.

The primary analysis occurred after all randomized subjects completed PTW 12 or prematurely discontinued from the study. If enrollment into the 12-week arm was discontinued for any reason, ongoing subjects in that arm were to have treatment extended to 24 weeks; these

subjects would be grouped with the 24-week arm in the efficacy and safety analyses. If the virologic rebound criterion was met and pegIFN/RBV add-on therapy offered, subjects who chose to add-on pegIFN/RBV treatment were removed from the analysis and summarized separately.

Other efficacy endpoints included:

- Comparison of the percentage of subjects with $SVR_{12}$ between the two arms
- Percentage of subjects who experience virologic failure and relapse

In addition, the primary endpoints within Arm A were tested separately from Arm B to determine superiority and non-inferiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy.

**Assessment of Virologic Failure across Phase 3 Program**

In all the Phase 3 trials, the following criteria were used to determine evidence of on-treatment virologic failure:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment;
- Failure to achieve HCV RNA < LLOQ by Week 6;
- Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

**General Inclusion/Exclusion Criteria**

In addition to the study-specific inclusion criteria described above, the following inclusion/exclusion criteria applied to all of the Phase 3 trials.

- **General Inclusion Criteria:**

Ribavirin, which is a teratogen was used in all the Phase 3 trials. Therefore, the following recommendations related to pregnancy prevention were enforced:

- Females who were:
  - Not of childbearing potential, defined as:
    - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state),
    - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), or
    - sexually active with female partners only.
  - of childbearing potential and sexually active with male partner(s) currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs (as outlined in the subject informed consent or other subject information documents), starting with Study Day 1 and for 7 months after stopping study drug as directed by the local ribavirin label.

Female subjects of childbearing potential must be willing to use two effective forms of birth control while receiving study drug (oral contraceptives or contraceptives containing ethinyl estradiol are not considered effective during study drug treatment). The subject must also be abstinent from sexual intercourse or be willing to use two effective forms of birth control for 7 months (or per local ribavirin label) after stopping study drugs.

- Females were to have negative results for pregnancy tests performed:
  -at Screening by serum specimen within 35 days prior to initial study drug administration, and
  -at Baseline (prior to dosing) by urine specimen.
- Males must have been abstinent from sexual intercourse, surgically sterile or agree to practice two effective forms of birth control from those listed below, throughout the course of the study, starting with Study Day 1 and for 7 months after the last dose of study drug (or per local RBV label):
  -Partner(s) using an IUD, or
  -Partner(s) using oral, injected, or implanted methods of hormonal contraceptives, or
  -Subject and/or partner(s) using condoms, contraceptive sponge or diaphragm with spermicidal jellies or creams.

***Reviewer comment: Due to excessive transaminitis in female subjects and healthy volunteers, contraceptives containing ethinyl estradiol were not considered effective during administration of study drugs and their use was not allowed.***

- **General Exclusion Criteria:**

Based on previous interactions with ritonavir as well as drug-drug interaction studies conducted with the DAAs:

- The following medications were contraindicated for use:
  Alfuzosin, Amiodarone, Astemizole, Bepridil, Carbamazepine, Cisapride, Dronedarone, Efavirenz, Eleptriptan, Eplerenone, Ergot derivatives, Fusidic Acid, Gemfibrozil, Lovastatin, Midazolam (oral), Mifepristone, Modafinil, Montelukast, Nefazodone, Phenobarbital, Phenytoin, Pimozide, Pioglitazone, Propafenone, Quercetin, Quinidine, Rifabutin, Rifampin, Rosiglitazone, Salmeterol, Simvastatin, St. John's Wort, Telithromycin, Terfenadine, Triazolam, Trimethoprim, Troglitazone, Troleandomycin,, Buprenorphine, Clarithromycin, Conivaptan, Everolimus,Itraconazole, Ketoconazole, Methadone or Voriconazole
- Use of any of the following medications was also contraindicated because dose adjustments could not be made:
  Alfentanil, Budesonide, Clarithromycin, Colchicine, Cyclosporine, Digoxin, Disopyramide, Divalproex, Erythromycin, Ethosuximide, Fentanyl, Fluticasone, Lamotrigine, Lidocaine (use for local anesthesia is permitted), Mexiletine, Perphenadine, Risperadone, Sildenafil, Sirolimus, Tacrolimus (use topically is permitted), Tadalafil, Thioridazine, Vardenafil, Vinblastine, Vincristine, Warfarin
- Use of known strong inhibitors of cytochrome P450 3A (CYP3A), CYP2C8 (e.g., gemfibrozil, montelukast) or inducers of CYP3A (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) within 2 weeks or within 10 half-lives of the respective medication prior to study drug administration.
- Use of herbal supplements, including milk thistle
- Use of hormonal contraceptives

- Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result associated with documented short-term use or chronic stable use of a prescribed medication in that class or a single positive result for alcohol.
- Any cause of liver disease other than chronic HCV infection
- Screening laboratory analyses showing any of the following abnormal laboratory results:
  -ALT > 5 × ULN
  -AST > 5 × ULN
  -Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
  -Albumin < LLN
  -Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study-Designated Physician
  -Hemoglobin < LLN
  -Platelets <120,000 cells per $mm^3$
  -Absolute neutrophil count (ANC) <1500 cells/µL
  -Indirect bilirubin >1.5 × ULN and direct bilirubin > ULN
- Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or Study Day 1 (prior to dosing).
- History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
- History of solid organ transplantation.

# 6 Review of Efficacy

## ***Efficacy Summary***

## 6.1 Indication

The Applicants' proposed indication read:

- (b) (4)

### 6.1.1 Methods

Data from 6 Phase 3 trials were submitted to support the proposed indications. All of the trials enrolled only GT1-infected adults, so it was possible to pool demographic data across trials. The primary efficacy review was conducted by the Statistical reviewer, Dr. Joy Mele, with input from the Virology reviewer, Dr. Patrick Harrington, and myself.

## 6.1.2 Demographics

While each trial had a number of study-specific inclusion criteria, the main inclusion/exclusion criteria were comparable across the Phase 3 trials (see above).

Compared to the general US population infected with HCV, subjects in the PBO- and Regimen-Controlled trials were generally younger (51.5 compared to 54 years of age), more female (44% compared to 35%), and overwhelmingly White (90% compared to 65%). Subjects in the Compensated Cirrhosis trial were primarily White males. African Americans/Blacks are over-represented in the general population of US patients with chronic HCV infection (~23% of infected persons) and tend to respond less well to currently available therapies. However, only 6% of enrollees in the Phase 3 trials were Black/African American. Unfortunately, the representation of this important subgroup was minimal.

- **PBO Controlled Trials**

In general the subjects enrolled in the PBO-Controlled Trials represented a relatively healthy population as there were no subjects with advanced disease or decompensated liver function. Overall, subjects were white (90%), males (56%) with a mean age of 50.9 years. The majority of subjects were treatment-naïve (62%) with minimal fibrosis (73%), 19% prior pegIFN/RBV null responders, 64% were infected with HCV GT1a and 36% with GT1b. A total of 77% of subjects had a non-CC IL28B genotype: 59% genotype CT and 18% genotype TT.

**Table 9 Demographic and disease characteristics, PBO-Controlled trials**

| | M11-646 | | M13-098 | |
|---|---|---|---|---|
| | 3-DAA + RBV N=473 | PBO N=158 | 3-DAA + RBV N=297 | PBO N=97 |
| Age: mean±SD | 49.4±10.98 | 51.2±10.23 | 51.7 ± 10.26 | 54.9±8.46 |
| -<55 | 290 (61%) | 85 (54%) | 159 (53.5%) | 42 (43%) |
| ->55-<65 | 164 (35%) | 63 (40%) | 119 (40%) | 42 (43%) |
| ->65 | 19 (4%) | 10 (6%) | 20 (7%) | 13 (13%) |
| Sex | | | | |
| -Male | 271 (57%) | 73 (46%) | 167 (52%) | 60 (62%) |
| -Female | 202 (43%) | 85 (54%) | 130 (40%) | 37 (38%) |
| Race | | | | |
| -White | 428 (90.5%) | 144 (91%) | 269 (91%) | 86 (89%) |
| -Black/African American | 26 (5.5%) | 8 (5%) | 22 (7%) | 10 (10%) |
| -Asian | 11 (2%) | 3 (2%) | 6 (2%) | 0 |
| -American Indian/Alaska Native | 3 (<1%) | 1 (<1%) | 0 | 0 |
| -Hawaiian/Pacific Islander | 1 (<1%) | 1 (<1%) | 0 | 0 |
| -Mixed | 4 (1%) | 1 (<1%) | 0 | 1 (1%) |
| Ethnicity: Hispanic/Latino | 27 (6%) | 5 (3%) | 22 (7%) | 3 (3%) |
| BMI ≥30 kg/m$^2$ | 71 (15%) | 31 (20%) | 59 (20%) | 19 (20%) |
| Weight (kgs): mean±SD | 75.7±15.45 | 76.2±15.56 | 77.6 ±15.04 | 77.7±15.01 |
| Baseline $log_{10}$ HCV RNA (SD) | 6.40 (0.62) | 6.47 (0.65) | 6.55 (0.54) | 6.52 (0.48) |
| RNA ≥800,000 IU/mL | 369 (78%) | 130 (82%) | 255 (86%) | 88 (91%) |
| Mean baseline ALT (U/L) | 68.5 | 63.5 | 64.4 | 64.9 |
| Baseline fibrosis stage | | | | |
| -F0-F1 | 363 (77%) | 116 (73%) | 202 (68%) | 65 (67%) |
| -F2 | 70 (15%) | 27 (17%) | 53 (18%) | 17 (17.5%) |
| -F3 | 40 (8%) | 15 (9%) | 42 (14%) | 15 (15.5%) |
| HCV Genotype 1 subtype | | | | |
| -GT 1a | 322 (68%) | 105 (66.5%) | 173 (58%) | 57 (59%) |
| -GT 1b | 151 (32%) | 53 (33.5%) | 123 (41%) | 40 (41%) |
| -Other | - | - | 1 (<1%) | 0 |
| Baseline IP-10 (NG/L) | | | | |
| -<600 | 375 (79%) | 118 (75%) | 199 (72%) | 70 (74%) |

| | | | | |
|---|---|---|---|---|
| -≥600 | 66 (14%) | 31 (20%) | 77 (28%) | 25 (26%) |
| -Missing | 32 (7%) | 9 (6%) | 21 (7%) | 2 (2%) |
| IL28B Genotype | | | | |
| -CC | 144 (30%) | 50 (32%) | 34 (11%) | 7 (7%) |
| -CT | 254 (54%) | 82 (52%) | 200 (67%) | 70 (72%) |
| -TT | 75 (16%) | 26 (16.5%) | 63 (21%) | 20 (21%) |
| History of diabetes mellitus | 19 (4%) | 5 (3%) | 14 (5%) | 4 (4%) |
| HOMA IR ≥ 3 mU × mmol/$L^2$ | 58 (16%) | 19 (17%) | 56 (24.5%) | 16 (22.5%) |
| History of depression/bipolar | 60 (15%) | 26 (16.5%) | 68 (23%) | 13 (13%) |
| History of bleeding disorder | 6 (1%) | 4 (2%) | 5 (2%) | 2 (2%) |
| Geographic region | | | | |
| -North America | 229 (48%) | 73 (46%) | 136 (46%) | 33 (34%) |
| -Europe | 211 (45%) | 71 (45%) | 150 (50.5%) | 61 (63%) |
| -Australia/New Zealand | 33 (7%) | 14 (9%) | 11 (4%) | 3 (3%) |
| Former injection drug use | 205 (44%) | 59 (37%) | 90 (30.5%) | 28 (29%) |
| Type of prior pegIFN/RBV response | | | | |
| -Prior null | | | 146 (49%) | 47 (48.5%) |
| -Prior partial | N/A | N/A | 65 (22%) | 21 (22%) |
| -Prior relapser | | | 86 (29%) | 29 (30%) |

- **Regimen-Controlled Trials**

The demographic and disease characteristics of subjects in the Regimen-Controlled Trials were generally similar between treatment groups, with no clinically relevant differences identified.

The majority of subjects were White (90%); 51% were male and the mean age was 50.8 years. Overall, a total of 69 (8%) subjects were Black/African American; among subjects enrolled in the US, 68 (18%) were Black/African American. The majority of subjects were treatment-naïve (80%) with minimal fibrosis (67%), 7% were prior pegIFN/RBV null responders, 34% were infected with HCV GT1a (Study M14-002) and 66% with GT1b (Studies M13-389 and M13-961); this contrasts with the PBO-Controlled Trials, in which 64% of subjects were infected with HCV GT1a and 36% with GT1b. Overall, 78% of subjects had an IL28B genotype that was non-CC; 60% of subjects had IL28B genotype CT and 18% had IL28B genotype TT.

**Table 10 Demographic and disease characteristics, Regimen-Controlled trials**

| | **M14-002** | | **M13-389** | | **M13-961** | |
|---|---|---|---|---|---|---|
| | **3-DAA + RBV N=100** | **3-DAA N=205** | **3-DAA + RBV N=91** | **3-DAA N=95** | **3-DAA + RBV N=210** | **3-DAA N=209** |
| Age: mean±SD | 51.6±10.99 | 51.2±10.23 | 54.2±10.90 | 54.2±10.51 | 48.4±11.94 | 49.2±12.03 |
| -<55 | 52 (52%) | 109 (53%) | 37 (41%) | 43 (45%) | 129 (61%) | 133 (64%) |
| -≥55-<65 | 38 (38%) | 83 (40%) | 39 (43%) | 36 (38%) | 67 (32%) | 57 (27%) |
| -≥65 | 10 (10%) | 13 (6%) | 15 (16.5%) | 16 (17%) | 14 (7%) | 19 (9%) |
| Sex | | | | | | |
| -Male | 70 (70%) | 129 (63%) | 49 (49.5%) | 57 (60%) | 106 (50.5%) | 86 (41%) |
| -Female | 30 (30%) | 76 (37%) | 46 (50.5%) | 38 (40%) | 104 (49.5%) | 123 (59%) |
| Race | | | | | | |
| -White | 86 (86.5%) | 171 (83%) | 84 (92%) | 86 (90.5%) | 198 (94%) | 196 (94%) |
| -Black/African American | 10 (10%) | 26 (10%) | 3 (3%) | 6 (6%) | 10 (5%) | 10 (5%) |
| -Asian | 1 (1%) | 3 (1.5%) | 1 (1%) | 2 (2%) | 1 (<1%) | 1 (<1%) |
| -American Indian/Alaska Native | 3 (3%) | 1 (<1%) | 1 (1%) | 0 | 0 | 0 |
| -Hawaiian/Pacific Islander | 0 | 1 (<1%) | 0 | 0 | 0 | 0 |
| -Mixed/Other | 0 | 2 (1%) | 2 (2%) | 1 (1%) | 1 (<1%) | 1 (<1%) |
| -Missing | 0 | 0 | 0 | 0 | 0 | 1 |
| Ethnicity: Hispanic/Latino | 10 (10%) | 18 (9%) | 4 (4%) | 2 (2%) | 2 (1%) | 5 (2%) |
| BMI ≥30 kg/$m^2$ | 71 (15%) | 39 (19%) | 18 (20%) | 22 (23%)* | 28 (13%) | 41 (20%) |
| Weight (kgs): mean±SD | 81.0±15.52 | 76.2±15.56 | 74.6±12.89 | 79.7±16.99* | 74.1±13.83 | 74.6±15.29 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Baseline $log_{10}$ HCV RNA (SD) | 6.64 (0.50) | 6.53 (0.68) | 6.56 (0.56) | 6.48 (0.53) | 6.29 (0.77) | 6.33 (0.72) |
| RNA ≥800,000 IU/mL | 92 (92%) | 172 (84%) | 78 (86%) | 86 (90.5%) | 159 (76%) | 148 (71%) |
| Mean baseline ALT (U/L) | 69.7 | 74.8 | 58.6 | 63.8 | 66.9 | 63.8 |
| Baseline fibrosis stage | | | | | | |
| -F0-F1 | 63 (63%) | 132 (64%) | 64 (70%) | 61 (64%) | 150 (71%) | 141 (67%) |
| -F2 | 21 (21%) | 35 (17%) | 13 (14%) | 21 (22%) | 38 (18%) | 47 (23%) |
| -F3 | 16 (16%) | 38 (18.5%) | 14 (15%) | 13 (14%) | 22 (11%) | 20 (10%) |
| HCV Genotype 1 subtype | | | | | | |
| -GT 1a | 100 (100%) | 204 (99.5%) | 2 (2%) | 1 (1%) | N/A | N/A |
| -GT 1b | N/A | 1 (0.5%) | 89 (98%) | 93 (98%) | 210 (100%) | 209 (100%) |
| -Other | 0 | 0 | 0 | 1 (1%) | 0 | 0 |
| Baseline IP-10 (ng/L) | | | | | | |
| -<600 | 81 (85%) | 157 (83%) | 60 (71%) | 65 (73%) | 163 (82%) | 161 (80.5%) |
| ->600 | 14 (15%) | 32 (17%) | 25 (29%) | 24 (27%) | 35 (18%) | 39 (19.5%) |
| -Missing | 5 | 16 | 6 | 6 | 12 | 9 |
| IL28B Genotype | | | | | | |
| -CC | 31 (31%) | 63 (31%) | 10 (11%) | 7 (7%) | 44 (21%) | 44 (21%) |
| -CT | 58 (58%) | 105 (51%) | 59 (65%) | 88 (93%) | 127 (60%) | 132 (63%) |
| -TT | 11 (11%) | 37 (18%) | 22 (24%) | 0 | 39 (19%) | 33 (16%) |
| History of diabetes mellitus | 5 (5%) | 10 (5%) | 9 (10%) | 10 (10.5%) | 8 (4%) | 9 (4%) |
| HOMA IR ≥ 3 mU × mmol/$L^2$ | 59 | 115 | 21 (29%) | 27 (35.5%) | 35 (19%) | 44 (24%) |
| History of depression/bipolar | 17 (17%) | 46 (22%) | 17 (19%) | 9 (9.5%) | 20 (9.5%) | 19 (9%) |
| History of bleeding disorder | 0 (0%) | 1 (<1%) | 2 (2%) | 0 | 4 (2%) | 2 (1%) |
| Geographic region | | | | | | |
| -North America | 81 (81%) | 166 (81%) | 14 (15%) | 19 (20%) | 48 (23%) | 47 (22.5%) |
| -Europe/United Kingdom | 8 (8%) | 19 (9%) | 77 (85%) | 76 (80%) | 162 (77%) | 162 (77.5%) |
| -Canada | 11 (11%) | 20 (10%) | 0 | 0 | 0 | 0 |
| -Australia/New Zealand | 0 | 0 | 0 | 0 | 0 | 0 |
| Type of prior pegIFN/RBV response | | | | | | |
| -Prior null | N/A | N/A | 32 (35%) | 33 (35%) | N/A | N/A |
| -Prior partial | | | 26 (29%) | 27 (28%) | | |
| -Prior relapser | | | 33 (36%) | 35 (37%) | | |

- **Compensated Cirrhosis Trial**

Subjects in this trial represented a population of cirrhotic subjects with mild hepatic impairment ("compensated cirrhosis"). The disease and demographic data from this trial are presented in the following table. Subjects were nearly all White (92%), male (70%), and had a median age of 58 years. Forty-two percent were treatment-naïve. All subjects had Child-Pugh score ≤6 with no evidence of hepatic decompensation. Sixty-nine percent of subjects had GT1a infection and 31% had GT1b infection. Again, there was significant under representation of Black/African Americans in this trial.

**Table 11 Demographic and disease characteristics, Compensated Cirrhosis trial**

| | **3-DAA + RBV x 12 weeks N=208** | **3-DAA + RBV x 24 weeks N=172** |
|---|---|---|
| Age: mean (±SD) | 57.1 (±7.01) | 56.5 (±7.87) |
| -<55 | 58 (28%) | 60 (35%) |
| ->55 - <65 | 124 (60%) | 89 (52%) |
| ->65 | 26 (12.5%) | 23 (13% |
| Sex | | |
| -Male | 146 (70%) | 121 (70%) |
| -Female | 62 (30%) | 51 (30%) |
| Race | | |
| -White | 199 (96%) | 161 (94%) |
| -Black/African American | 6 (3%) | 6 (3%) |
| -Asian | 3 (1%) | 5 (3%) |
| -American Indian/Alaska Native | 0 | 0 |
| -Hawaiian/Pacific Islander | 0 | 0 |

| | | |
|---|---|---|
| -Mixed/Other | 0 | 0 |
| Ethnicity<br>-Hispanic or Latino | <br>25 (12%) | <br>20 (12%) |
| BMI ≥30 kg/m$^2$ | 62 (30%) | 46 (27%) |
| RNA ≥800,000 IU/mL | 174 (84%) | 153 (89%) |
| Mean baseline ALT (U/L) | 99.4 | 99.7 |
| Childs Pugh<br>-5<br>-6<br>->6 | <br>170 (82%)<br>38 (18%)<br>0 | <br>140 (81%)<br>27 (16%)<br>5 (3%) |
| HCV Genotype subtype<br>-GT 1a<br>-GT 1b | <br>140 (67%)<br>68 (33%) | <br>121 (70%)<br>51 (30%) |
| Type of prior pegIFN/RBV response<br>-Naïve<br>-Prior null<br>-Prior partial<br>-Prior relapse | <br>86 (41%)<br>75 (36%)<br>18 (9%)<br>29 (14%) | <br>74 (43%)<br>62 (36%)<br>13 (8%)<br>23 (13%) |
| Baseline IP-10 (ng/L)<br>-<600<br>->600<br>-Missing | <br>117 (62%)<br>72 (38%)<br>47 | <br>98 (63%)<br>58 (37%)<br>16 |
| History of diabetes mellitus | 29 (14%) | 31 (18%) |
| HOMA IR ≥ 3 mU × mmol/L$^2$ | 81 (50%) | 89 (64%) |
| History of depression/bipolar disorder | 51 (24.5%) | 43 (25%) |
| History of bleeding disorder | 5 (2%) | 4 (2%) |
| Geographic region<br>-United States<br>-Europe | <br>105 (50.5%)<br>103 (49.5%) | <br>93 (54%)<br>79 (46%) |

## 6.1.3 Subject Disposition

The following table shows the combined disposition of study subjects in the Phase 3 program. Overall 97.5% of subjects completed their entire course of assigned study drug treatment.

- **PBO-Controlled Trials**

Across the two PBO-controlled trials, 1031 subjects (774 3-DAA + RBV, 257 PBO) were enrolled and randomized; of these 1025 were treated in the Double-Blind (DB) treatment period, and 1009 (98%) completed study drug dosing. The most common reason for premature discontinuation of study drugs was adverse events, which occurred more often among subjects in the active treatment groups. The disposition of randomized subjects in the two PBO-controlled trials is shown in Table 12.

**Table 12 Subject disposition, Placebo-Controlled Trials**

| | **M11-646** | | **M13-098** | |
|---|---|---|---|---|
| | **3-DAA + RBV** | **PBO** | **DAA + RBV** | **PBO** |
| Number randomized | 477 | 159 | 297 | 98 |
| Number treated | 473 | 158 | 297 | 97 |
| Completed double-blind treatment | 464 (98%) | 157 | 292 (98%) | 96 |
| Discontinued double-blind treatment | 9 | 1 | 5 | 1 |
| -Adverse event | 3* | 1 | 3 | 0 |
| -Virologic failure | 0 | 0 | 0 | 0 |
| -Consent withdrawal | 3 | 0 | 1 | 1 |
| -Non-compliance | 1 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| -Lost to follow-up | 2 | 0 | 0 | 0 |
| -Other | 0 | 0 | 1 | 0 |

*Subject 383207 in Arm A of Study M11-646 was initially classified as "Other" and changed to "Adverse Event" because he interrupted study drugs for >7 days while hospitalized for an SAE, and could not restart medications per protocol.

Following completion of the DB treatment period, subjects initially randomized to PBO were offered open label (OL) treatment with the 3-DAA + RBV. One-hundred fifty seven and 96 subjects in Study M11-646 and M13-098, respectively, entered OL treatment and 9 subjects prematurely discontinued study drugs for adverse events (4), virologic failure (2), non-compliance (1), and consent withdrawal (2).

Typical reasons cited for withdrawal of consent and other reasons included the subject could not swallow study medication, the subject did not want to take study drugs any longer, the subject did not wish to continue in the study, the subject did not want to take an HIV medication, and the subject could no longer return for study visits. A total of 1003 subjects are in ongoing post-treatment follow-up.

- **Regimen-Controlled Trials**

There were 911 subjects randomized in the three Regimen-Controlled Trials; 910 received at least one dose of study drugs and 98% completed their assigned treatment. The primary difference between treatment groups was due to more virologic failures among GT1a subjects treated with the 3-DAA alone in Study M14-002. Across the three trials, 887 subjects remain in post-treatment follow-up.

**Table 13 Subject disposition, Regimen-Controlled Trials**

| | **3-DAA + RBV** | **3-DAA** |
|---|---|---|
| Number randomized | 402 | 509 |
| Number treated | 401 | 509 |
| Number completed study drugs | 397 (99%) | 497 (97%) |
| Discontinued study drugs | 3 | 12 |
| -Adverse events | 2 | 2 |
| -Virologic failure | 0 | 6 |
| -Withdrew consent | 1 | 1 |
| -Lost to follow-up | 0 | 3 |
| -Other | 0 | 2 |

In Study M13-389 there were seven subjects who were randomized and treated but were not included in the ITT GT1b efficacy subset: three with HCV GT1a, three with GT1b who were enrolled before Protocol Amendment No. 5 and not administered ABT-450/r/ABT-267 co-formulated drug, and one whose HCV subgenotype was not determined by the central laboratory.

- **Compensated Cirrhosis Trial**

Three-hundred eighty-one subjects were randomized, 380 were treated, and 367 (97%) completed study drug treatment. Adverse events in both groups and virologic failure in the 24-week group accounted for the majority of premature study drug discontinuations.

**Table 14 Subject disposition, Compensated Cirrhosis trial**

| | 3-DAA + RBV x 12 weeks | 3-DAA + RBV x 24 weeks |
|---|---|---|
| Number randomized | 209 | 172 |
| Number treated | 208 | 172 |
| Number completed study drug | 204 (98%) | 163 (95%) |
| Discontinued study drug | 4 | 9 |
| -Adverse event | 4 | 4 |
| -Non-compliance | 0 | 1 |
| -Virologic failure | 0 | 3 |
| -Other | 0 | 1[1] |

1. Subject incarcerated and could not receive study drugs

The study results were submitted once all subjects had completed 12 weeks of post-treatment follow-up and assessed for $SVR_{12}$. There are 203 and 167 subjects in the 12- and 24-week arms, respectively, in ongoing follow-up.

## 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for all six Phase 3 trials was $SVR_{12}$, defined as undetectable HCV RNA 12 weeks following intake of last actual dose of study medication using the Roche COBAS TaqMan® real-time reverse transcriptase PCR (RT-PCR) assay v. 2.0 (LLOQ 25 IU/mL, LLOD 15 IU/mL) to assess HCV RNA levels. All efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study drug. Please also refer to Dr. Joy Mele's Statistical Review for additional details.

- **PBO-Controlled Trials**

The primary outcome measure in the two PBO-controlled trials was non-inferiority of Arm A (3-DAA + RBV) to the historical rate for non-cirrhotic GT1-infected treatment naïve or treatment-experienced subjects treated with telaprevir plus pegIFN/RBV.

$SVR_{12}$ and 95% confidence interval (CI) data from subjects initially randomized to the 3-DAA + RBV regimens (Arm A of each trial) were included in the analyses, and presented herein. A follow-up analysis is planned after subjects initially randomized to PBO placebo who then received OL treatment complete through post-treatment Week 12 or premature discontinuation of the study, and these data will be the subject of a post-approval commitment.

The $SVR_{12}$ rates for the active treatment groups in the two placebo-controlled trials conducted in treatment-naïve (M11-646) and treatment-experienced (M13-098) non-cirrhotic subjects are shown in the following table.

**Table 15 $SVR_{12}$ rates, Placebo-Controlled trials**

| n/N (%) | 3-DAA + RBV |
|---|---|
| **M11-646 (all)** | 456/473 (96) |
| -GT1a naïve | 308/322 (96) |
| -GT1b naïve | 148/151 (98) |
| **M13-098 (all)** | 286/297 (96) |
| -GT1a experienced | 166/173 (96) |
| -prior null | 83/87 (95) |
| -prior partial | 36/36 (100) |
| -prior relapse | 47/50 (94) |
| -GT1b experienced[1] | 120/124 (97) |

| | |
|---|---|
| -prior null | 56/59 (95) |
| -prior partial | 29/29 (100) |
| -prior relapse | 35/36 (97) |

1 Includes one subject who could not be subtyped

In Study M11-646, the lower bound of the 95% CI for the $SVR_{12}$ had to be greater than 70% in order for the regimen to be considered non-inferior to the historical telaprevir-based therapy, and greater than 80% for the regimen to be superior. $SVR_{12}$ was achieved by 455/473 (96%) subjects, with a 95% CI of 94.5% to 97.9%. The lower confidence bound (LCB) was above 80%; therefore, both primary endpoints were achieved, and the 3-DAA + RBV regimen demonstrated both non-inferiority and superiority to the historical control rate for telaprevir-based therapy.

In Study M13-098, the percentage of subjects with $SVR_{12}$ in Arm A would be considered non-inferior to the historical rate for telaprevir/pegIFN/RBV if the lower bound of the 95% CI for $SVR_{12}$ was greater than 60%, and considered superior if greater than 70%. $SVR_{12}$ was achieved by 286/297 (96%) subjects, with a 95% CI of 94.1% to 98.4%; thus, the regimen demonstrated both non-inferiority and superiority to the historical control rate for telaprevir-based therapy.

In Study M11-646, 14 GT1a subjects failed to achieve an $SVR_{12}$ compared to 3 GT1b subjects. Reasons for non-response in the GT1a subjects were on-treatment virologic failure (1), relapse (6), and other reasons such as premature discontinuation and missing $SVR_{12}$ data (7). Among the GT1b subjects, 1 subject relapsed and two failed due to other reasons. In Study M13-098, 5 GT1a and 2 GT1b subjects relapsed, and 2 of each subtype prematurely discontinued study medications.

***Reviewer comment: The primary endpoint analysis of both PBO-controlled trials supports the conclusion that the 3-DAA + RBV regimen was superior to both placebo and treatment with telaprevir/pegIFN/RBV.***

- **Regimen-Controlled Trials**

The regimen-controlled trials were designed to assess the requirement for RBV in various subgroups. One approach to this assessment was a comparison of the percentage of subjects with hemoglobin decrease during treatment between subjects treated in 3-DAA + RBV arms and the subjects treated in 3-DAA arms. The statistical analysis included a simple risk differences and accompanying 2-sided 95% CI for each study. Further, the noninferiority in $SVR_{12}$ rates of the 3 DAA regimen to 3 DAA + RBV regimen using a –10.5% margin was assessed by calculating the difference and 2-sided 95% CI across prior treatment experience.

Of note, there were six subjects in Study M13-389 who were excluded from the efficacy analyses because they received ABT-450/r and ombitasvir as individual components rather than the fixed dose combination of ABT-450/r/ombitasvir. The overall $SVR_{12}$ rates for each of the Regimen-Controlled trials, by treatment experience, are shown in Table 16.

**Table 16 $SVR_{12}$ rates, Regimen-Controlled trials**

| n/N (%) | 3-DAA + RBV | 3-DAA |
|---|---|---|
| M13-389 GT1b experienced (all) | **86/88 (98)** | **91/91 (100)** |
| -prior null | 30/31 (97) | 32/32 (100) |
| -prior partial | 24/25 (96) | 26/26 (100) |
| -prior relapse | 32/32 (100) | 33/33 (100) |
| M13-961 GT1b treatment naive | **208/210 (99.5)** | **209/209 (100)** |
| M14-002 GT1a treatment naïve | **96/100 (97)** | **183/204[8] (90)** |

*Excludes one HCV GT1b subject who enrolled due to protocol error (enrolled based on local laboratory result).

In all three trials, superiority was achieved for both regimens to the historical control rate for telaprevir/peg-IFN/RBV therapy (LCB for the 95% CI greater than 75%).

In Studies M13-389 and M13-961, the 3-DAA arms were also non-inferior to the 3-DAA + RBV arm. In Study M14-002 there the $SVR_{12}$ rate for the 3-DAA + RBV arm was statistically significantly higher than the rate in the 3-DAA alone arm. Further, non-inferiority of the 3-DAA regimen to the 3-DAA + RBV regimen was not achieved as the lower bound of the 95% CI was -12.0%, which was below the pre-specified threshold of -10.5%.

Reasons for not achieving an $SVR_{12}$ in the three trials are shown in the following table.

**Table 17 Reasons for non-response, Regimen-Controlled trials**

| | 3-DAA + RBV | 3-DAA |
|---|---|---|
| M13-389 GT 1b experienced | | |
| -Other failures[1] | 2 | 0 |
| M13-961 GT 1b treatment naive | | |
| -On-treatment virologic failure | 1 | 0 |
| -Other failures[1] | 1 | 0 |
| M14-002 GT 1a treatment naïve | | |
| -On-treatment virologic failure | 1 | 6 |
| -Relapse | 1 | 10 |
| -Other failures[1] | 2 | 5 |

1. Other failures include premature discontinuation, missing $SVR_{12}$ data

***Reviewer comment: The data demonstrate superiority of both the 3-DAA + RBV and 3-DAA regimens over the historical control, an increase in response rate among GT1a treatment naïve subjects treated with RBV versus no RBV, and no difference in $SVR_{12}$ rates in GT1b-infected subjects treated with and without RBV. Based on these conclusions, the recommendation for GT1a treatment naïve patients will be to receive RBV.***

- **Compensated Cirrhosis Trial**

The following table shows the $SVR_{12}$ rates. In this trial, 380 subjects were randomized to 12 weeks (n=208) or 24 weeks (n=172) of treatment with the 3-DAA + RBV. The primary endpoint was the comparison of $SVR_{12}$ between the two durations of treatment with calculation of a 2-sided 95% CI. For nearly all populations of subjects with GT1a, 24 weeks provided numerically better $SVR_{12}$ rates compared to 12 weeks of treatment.

**Table 18 $SVR_{12}$ rates, Compensated Cirrhosis trial**

| n/N (%) | 3-DAA + RBV x 12 weeks | 3-DAA + RBV x 24 weeks |
|---|---|---|
| -Overall | **191/208 (92)** | **166/172 (96)** |
| -GT1a all | **124/140 (89)** | **115/121 (95)** |
| -GT1b all | **67/68 (98)** | **51/51 (100)** |
| -GT 1a TN | **59/64 (92)** | **53/56 (96)** |
| -GT 1b TN | **22/22 (100)** | **18/18 (100)** |
| -GT 1a TE | **65/76 (86)** | **62/65 (96)** |
| -prior null | 40/50 (80) | 39/42 (93) |
| -prior partial | 11/11 (100) | 10/10 (100) |
| -prior relapse | 14/15 (93) | 13/13 (100) |
| -GT 1b TE | **45/46 (98)** | **33/33 (100)** |
| -prior null | 25/25 (100) | 20/20 (100) |
| -prior partial | 6/7 (86) | 3/3 (100) |
| -prior relapse | 14/14 (100) | 10/10 (100) |

One of seven GT1b prior partial responders in the 12-week arm relapsed. The overall numbers of GT1b subjects was very small, which was likely attributable to fewer GT1b subjects failing prior peg-IFN/RBV therapy. With this single virologic failure being banded by 100% $SVR_{12}$ rates in prior null responders and relapsers, it is unlikely that extending the duration of treatment for this subgroup would impact response rates.

Among GT1a treatment naïve subjects, treatment for 24 weeks decreased virologic failure from four subjects to one, and for treatment experienced subjects, from nine to three subjects.

Each arm was tested to determine if it was non-inferior and/or superior to the historical $SVR_{12}$ rate for telaprevir/pegIFN/RBV. To be superior, the LCB of the 97.5% CI was to be above 54% and for non-inferiority it was to be above 43%; both arms demonstrated non-inferiority and superiority to telaprevir-based treatment.

***Reviewer comment: In subjects with GT1b infection, there was no advantage to longer treatment. For subjects with GT1a infection, 24 weeks of treatment produced generally positive results in all subjects. Relapse was the primary reason for not achieving SVR in the 12 week arm, which was reduced in the 24 week arm. Based on the small numbers of subjects, it is not possible to definitely select which types of GT1a patients should receive 12 weeks of treatment; therefore, treating all GT1a patients with 24 weeks of treatment may be most beneficial. The 24 week regimen provides best chance for response in subjects with GT1a as there are very limited options for those who fail.***

## 6.1.5 Analysis of Secondary Endpoints(s)

In each trial, multiple secondary endpoints were evaluated. The following endpoints were assessed as being the most clinically relevant that inform the recommendations for regimens and durations of treatment:

- Time to virologic suppression
- Virologic Failure (on-treatment virologic failure and relapse)
- IL28B genotype (CC or non-CC), (CC, CT, or TT) in treatment naïve subjects
- ALT normalization
- Percentage of subjects with hemoglobin decrease during treatment

***Reviewer comment: Other on-treatment endpoints such as rapid virologic response and end-of-treatment response were determined to not represent clinically relevant endpoints in the absence of achievement of SVR, and are not discussed further.***

**Time to Virologic Suppression**

Time to virologic suppression was defined as the study day of the first of two successive HCV RNA < LLOQ during the Treatment Period. Virologic suppression was rapid across all trials and subgroups with 99% of subjects <LLOQ by TW 4 and ~100% by TW 6.

**Virologic Failure**

The virologic failure population consisted of subjects with on-treatment virologic failure and/or relapse that did not discontinue study drugs for other reasons.

- On-treatment virologic failure was defined as a confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or persistent HCV RNA ≥ LLOQ during treatment with at least 6 weeks (≥ 36 days) of treatment

- Relapse was defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the $SVR_{12}$ assessment time point) among subjects with HCV RNA < LLOQ at the final treatment visit).

Across the Phase 2 and 3 program, 63/2414 (2.6%) subjects treated with the 3-DAA for 12 or 24 weeks (2%) experienced virologic failure: 58/1307 (4.4%) had GT1a and 5/1107 (0.5%) had GT1b (all post-treatment relapses). Among virologic failure subjects with GT1a treated for 12- or 24-weeks, 17 (29%) had on-treatment failure and 41 (71%) relapsed.

Specifically, in Study M14-002, the addition of RBV appeared to be the only factor associated with a decrease in on-treatment failures (from 6 to 1) and relapses (from 10 to 1).

In Study M13-099, there was a numerical advantage in virologic failure rates noted for 24 weeks of treatment over 12 weeks of treatment in all prior treatment subgroups of GT1a-infected subjects: prior null 14% versus 7%, prior partial 9% versus 0%, and prior relapse 7% versus 0%.

Resistance testing demonstrated treatment-emergent substitutions in all three DAA targets, and the substitutions were those expected based on preclinical virologic testing. The most common treatment-emergent substitutions were (most common substitutions in bold):

NS3/4A:
- GT1a subjects: V36A/M/T, F43L, V55I, Y56H, Q80L, I132V, **R155K**, A156G, **D168x** (including A, F, H, I, L, N, T, V, Y), P334S, S342P, E357K, V406A/I, T449I, P470S
- GT1b subjects: **Y56H**, **D168A/V**, E357K, NS4A V23A

NS5A:

- GT1a subjects: K24R, **M28A/T/V**, **Q30E/K/R**, H58D/P/R, E62D, Y93C/N
- GT1b subjects: H54Y, **Y93H**

NS5B:

- GT1a subjects: G307R, C316Y, M414T, E446K/Q, A450V, A553T, G554S, **S556G/R**, G558R, D559G/I/N/V, Y561H, L588F
- GT1b subjects: C316Y, M414I, S556G (substitutions emerged in only 2 subjects)

Assessment of responses based on presence of pre-treatment resistance substitutions failed to identify any that predicted non-response, and as such prescreening is not recommended. For additional information, please see Dr. Patrick Harrington's Virology review.

***Reviewer comment: All resistance associated substitutions that were identified in subjects who had virologic failure were those known to be associated with resistance to each DAA. Pre-treatment screening for resistance mutations will not be required. Again, in non-cirrhotic GT1a subjects, the addition of RBV appeared to decrease the relapse rate among those treated with 3-DAA + RBV. Among cirrhotic (treatment experienced) subjects with GT1a infection, the virologic failure rates were reduced with longer duration treatment.***

**IL28B Genotype**

In 2009, numerous publications described a novel association between single nucleotide polymorphisms (SNPs) near the interleukin (IL) 28B gene locus and response to treatment in subjects with CHC. Using a GWAS to investigate 300,000 to 900,000 SNPs in each sample, the investigators identified a particular SNP (rs12979860) strongly determined the outcome of pegINF-based HCV therapy. Three genotypes were identified: CC, CT and TT.

IL28B genotype was assessed in treatment naïve non-cirrhotic subjects in studies M11-646, M13-961, and M14-002, and treatment naïve cirrhotic subjects in study M13-099 to determine the impact of different IL28B genotypes on response.

In treatment naïve, non-cirrhotic, GT1a-infected subjects, there was no difference in $SVR_{12}$ rates for those with the IL28B CC genotype; 96% and 97% for 3-DAA + RBV and 3-DAA alone, respectively. In the 4-month update, however, three subjects who received the 3-DAA alone relapsed between the $SVR_{12}$ and $SVR_{24}$ window, increasing the virologic failure rate to 8%.

In non-cirrhotic GT1a subjects with non-CC genotypes treated with 3-DAA + RBV, the $SVR_{12}$ rate was 95%, and when RBV was not included in the regimen the rate was lower at 87%, suggesting (1) RBV reduced the relapse rate, and (2) these subjects would benefit from the addition of RBV to their treatment regimen (see Table 18).

**Table 19 $SVR_{12}$ and virologic failure rates by IL28B genotype, GT 1a treatment naïve (non-cirrhotic) subjects, Study M11-646 and M14-002 pooled**

| | 3-DAA + RBV | 3-DAA |
|---|---|---|

| N (%) | $SVR_{12}$ | VF | $SVR_{12}$ | VF |
|---|---|---|---|---|
| **CC** | 133/137 (97) | 2 (3.5) | 60/63 (95) | 2 (3) |
| **CT** | 216/228 (95) | 5 (2) | 91/104 (87.5) | 11 (11) |
| **TT** | 55/57 (96) | 2 (3.5) | 32/37 (86.5) | 3 (8) |

$SVR_{12}$ data in GT1a treatment naive cirrhotic subjects with non-CC genotypes also suggest a benefit from 24 weeks over 12 weeks of treatment (see Table 19).

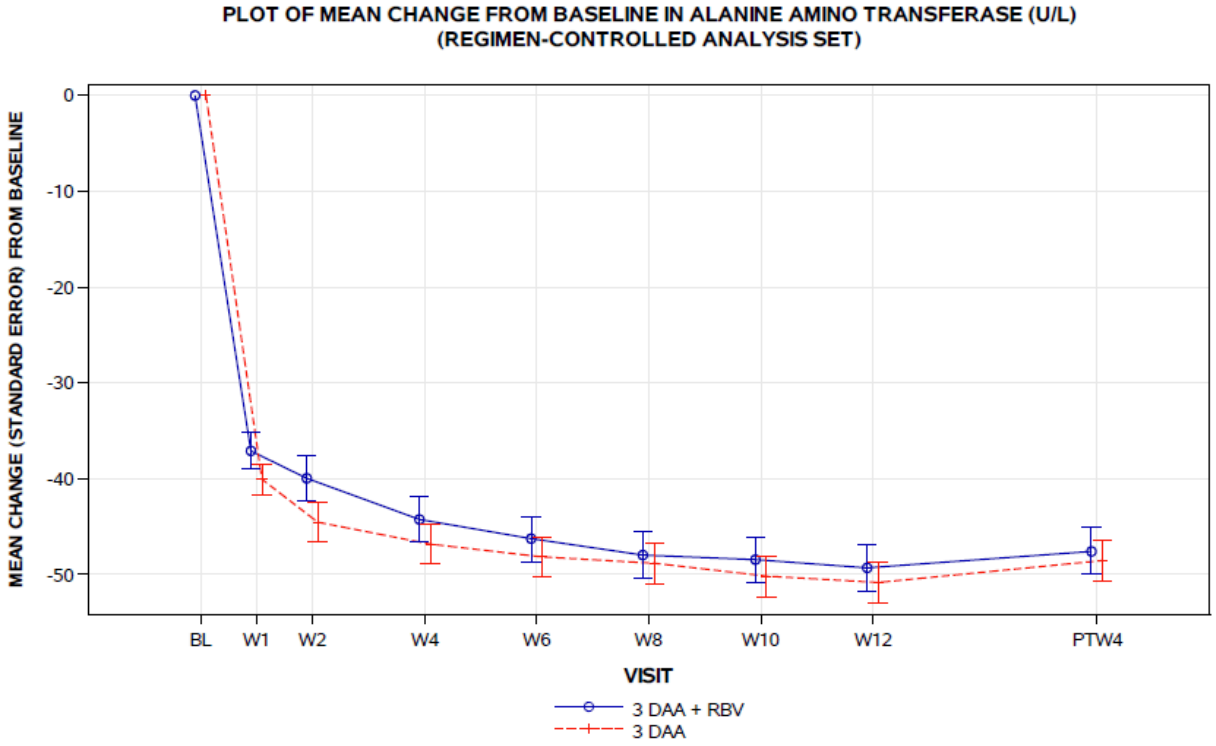
**Table 20 $SVR_{12}$ and virologic failure by IL28B genotype, GT1a treatment naïve (cirrhotic) subjects, Study M13-099**

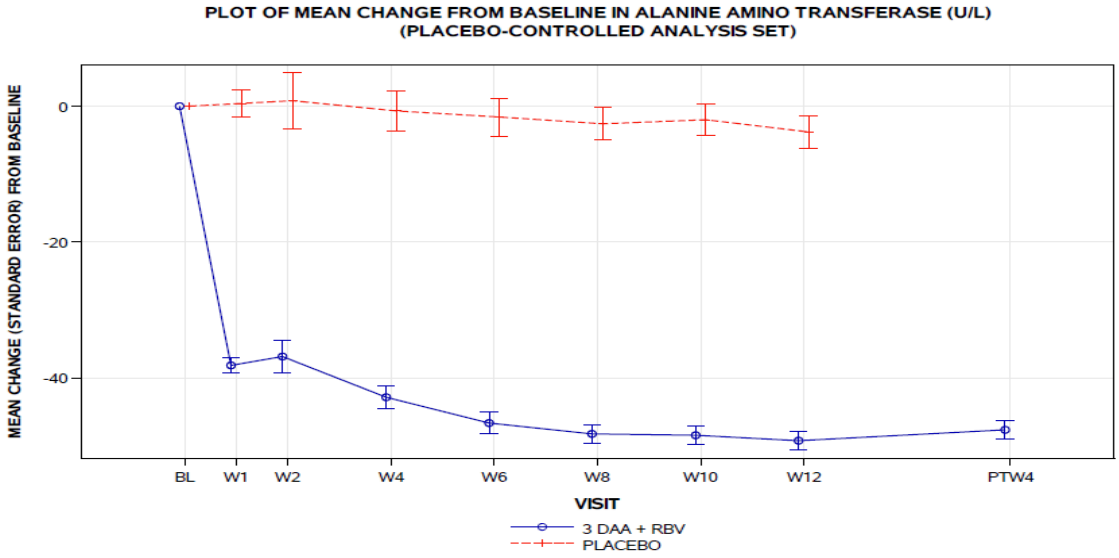
| | 3-DAA + RBV 12-Weeks | | 3-DAA + RBV 24-Weeks | |
|---|---|---|---|---|
| **N (%)** | **$SVR_{12}$** | **VF** | **$SVR_{12}$** | **VF** |
| **CC** | 19/19 (100) | 0 | 14/16 (87.5) | 0 |
| **CT** | 31/34 (91) | 3 (9) | 29/31 (93.5) | 1 (3) |
| **TT** | 9/11 (82) | 1 (9) | 8/9 (89) | 0 |

Treatment naïve GT1b subjects achieved $SVR_{12}$ rates 99% regardless of IL28B genotype or the inclusion of RBV in the regimen, and will not be discussed further. The 3-DAA + RBV regimen was the only regimen evaluated in GT1a treatment experienced non-cirrhotic subjects, and that will be the recommended regimen for this group.

## ALT Normalization

ALT was normalized in about 98% of patients taking 3-DAA + RBV (median decrease of about 47 U/L) compared to about 15% of placebo patients. As shown in the following two graphs, ALT levels underwent rapid declines were generally within normal limits by treatment weeks 8-10.




**Percentage of subjects with hemoglobin decrease during treatment**

In brief, as would be expected from the effect of RBV, a significant decrease in hemoglobin was observed in 3-DAA + RBV arms compared to the 3-DAA arms: -2.5 mg/dL versus -<1.0 mg/dL, respectively. RBV dose reductions due to anemia/low hemoglobin did not negatively impact SVR rates. Please see Section 7 below for more details on the safety ramifications of RBV-induced anemia.

### 6.1.6 Other Endpoints

(b) (4)

[redacted]

### 6.1.7 Subpopulations

Across the Phase 3 program, the following subgroups were evaluated:

- Sex (male versus female)
- Baseline HCV RNA level (≤ 800,000 IU/mL or >800,000 IU/mL);
- Baseline IP-10 (≤ 600 pg/mL or >600 pg/mL);
- Age (<65 versus ≥65 years);
- Race (Black versus non-Black);
- Ethnicity (Hispanic versus none);
- Geographic Region (North America, Europe/Australia);
- BMI (<30 or ≥30 $kg/m^2$);
- Subjects with RBV dose modifications (yes/no);
- History of Diabetes (yes/no);
- History of Bleeding Disorders (yes/no);
- Former IV drug user or subject on stable opiate substitution (yes/no);
- Baseline platelet count <90,000 and ≥90,000 x $10^9$/L and Child-Pugh Score (5 versus 6) (Study M13-099 only).

***Reviewer comment: The overall rate of virologic failure in the Phase 3 trials was low, and it was not possible to definitely identify, based on baseline characteristics, specific subpopulations of subjects that were either more or less likely to respond to treatment.***

***For the majority of the subpopulations evaluated, there were numerical increases in $SVR_{12}$ rates when RBV was added to the 3-DAA in GT1a treatment naïve subjects without cirrhosis, and when the duration of treatment was extended to 24 weeks in GT1a cirrhotic subjects.***

***Having diabetes, a HOMA-IR >3, a bleeding disorder, a history of depression/bipolar disorder, a high baseline IP-10 level, or being a former IV drug user were not predictive of response (or non-response) to treatment with 3-DAAs. Further, the trials reviewed in this NDA did not enroll sufficient numbers of these subpopulations*** (b) (4)

[redacted]

**Sex**

There was no significant difference in achievement of $SVR_{12}$ between males and females: 98% and 97%, respectively, in non-cirrhotic subjects, and 93.5% and 95%, respectively, in cirrhotic subjects. In study 14-002 males treated with RBV had an SVR rate of 96% compared to those who did not receive RBV, 88%. This finding was similar, but less pronounced, in females: 100% with RBV and 95% without RBV.

**Age**

Only 8% of enrollees in the Phase 3 trials were ≥65 years of age. In general, subjects <65 or ≥65 years of age and older had similar response rates: 96% and 96%, respectively. In GT1a treatment naïve non-cirrhotic subjects the addition of RBV numerically increased the response rate in subjects <65 years of age from 90% to 97%, and there was no difference in outcomes for those ≥65 years of age; 100% in both arms. Among cirrhotic subjects, the $SVR_{12}$ rate for those aged <65 years of age treated for 12 weeks was 91% and 95% for those treated for 24 weeks. Similarly, the response rate increased from 96% to 100% for those ≥65 years treated for 12 or 24 weeks.

**Race**

Only 6% of subjects in the Phase 3 trials were Black/African American. There were no differences in achievement of $SVR_{12}$ rates between Blacks and non-Blacks: 95% compared to 96%. In Study M14-002 the addition of RBV appeared to increase response rates among both Black/African American and non-Black/African American subjects. In Blacks, the $SVR_{12}$ rate was 100% with RBV versus 85% without RBV. In non-Black subjects the response rate was 97% versus 91%. In the Compensated Cirrhosis trial, Black subjects had higher response rates when treated for 24 weeks: 100% versus 83% for 12 weeks of treatment.

**Ethnicity**

Only 6.5% percent of subjects enrolled in the Phase 3 trials were of Hispanic/Latino ethnicity. Overall, 92% of Hispanic/Latino subjects achieved $SVR_{12}$ compared to 95% of non-Hispanic/Latino subjects. Again, in Study M14-002, the addition of RBV increased the response in Hispanic/Latino subjects from 89% to 100%, and in the Compensated Cirrhosis trial extending the duration of treatment from 12 to 24 weeks increased the response rate from 84% to 95%.

**Geographic Region**

Overall, there were only very small numeric differences in achievement of $SVR_{12}$ between subjects from North America and those from the rest of the world (Europe/Australia). Of note, in the Compensated Cirrhosis trial, one site in France drove the results among GT1a prior null responders. Compared to all nulls in the trial (80% for 12 weeks and 93% for 24 weeks), the $SVR_{12}$ rate at the France site were 29% for 12 weeks and 100% for 24 weeks of treatment; no plausible explanation for this difference could be identified.

**Body Mass Index**

There was a numeric difference in achievement of $SVR_{12}$ between subjects with high BMI ($\geq$30 $kg/m^2$) and low BMI (<30 $kg/m^2$): 97% and 93%; this difference did not reach statistical significance.

In Study M14-002: the addition of RBV increased $SVR_{12}$ rates in subjects with BMI <30 $kg/m^2$ (99% versus 92%) and BMI $\geq$30 $kg/m^2$ (90.5% versus 82%). A similar finding was observed in the Compensated Cirrhosis trial where extending duration of treatment increased SVR rates in subjects with both high and low BMI.

**Baseline HCV RNA**

In subjects with GT1b, low baseline HCV RNA (<800,000 IU/mL) or high baseline HCV RNA ($\geq$800,000 IU/mL) was not associated with differences in response rates regardless if RBV was or was not included in the regimen.

In the Compensated Cirrhosis trial, GT1a subjects with very high baseline viral load levels (>3,690,000 copies/mL) had a higher numerical response rate with 24 weeks of treatment (95%) compared to 12 weeks of treatment (84%); the difference did not reach statistical significance.

In Study M14-002, GT1a non-cirrhotic treatment naïve subjects with either low or high viral load had a numerically higher response rate when RBV was included in the regimen. Subjects with baseline HCV RNA <800,000 IU/mL achieved 100% (8/8) $SVR_{12}$ with RBV compared to 91% (30/33) without RBV. In subjects with $\geq$800,000 IU/mL at baseline 97% (89/92) achieved $SVR_{12}$ with RBV compared to 90% (155/172) without RBV.

**Baseline IP10 <600 ng/L**

Interferon gamma-induced protein 10 (IP-10) are elevated in patients chronically infected with HCV GT1 or GT4 who do not achieve a SVR after completion of antiviral therapy. IP-10 predicts the first days of elimination of HCV RNA ("first phase decline") during interferon/ribavirin therapy for all HCV genotypes. Non-interferon containing DAA therapy is usually associated with rapid decline in HCV RNA levels from baseline. Since interferon was not included in any treatment regimens, baseline IP-10 levels were not expected to predict response to DAA treatment. The response data from the Phase 3 trials confirmed this expectation as there was no difference in $SVR_{12}$ rates between subjects with IP-10 levels <600 ng/L (98%) or $\geq$600 ng/L (98%), regardless of GT1 subtype or prior pegIFN/RBV experience. Because baseline IP-10 levels were not predictive of response (or non-response), and has not been correlated with DAA treatment, information about this factor is not relevant and will not be included in the label.

**Baseline Fibrosis Score (non-cirrhotic subjects)**

Increasing severity of fibrosis and lack of RBV was associated with a lower response rate in subjects with GT1a. The overall $SVR_{12}$ rate for GT1a subjects with $\geq$F2 fibrosis was 97.5% when treated with RBV and 86% when RBV was not included in the regimen. There was no such difference observed in subjects with GT1b.

**Baseline HOMA-IR >= 3 MU mmol/L$^2$**

Elevated HOMA-IR levels are associated with insulin resistance and more often elevated in patients infected with GT3. There were no differences in achievement of $SVR_{12}$ between subjects who entered with high or low HOMA-IR scores. Further, no data on the number of subjects who entered the clinical trials with elevated HOMA-IR score and had a decrease to <3 MU x mmol/L$^2$ were included in the NDA, which might have indicated an improvement in this parameter.

**Subjects with RBV Dose Modifications**

Undergoing a RBV dose modification was not associated with a decrease in SVR rates. One-hundred eleven subjects in the Phase 3 trials treated with the 3-DAA + RBV regimen underwent a RBV dose modification due to adverse events; of these, 98.5% achieved an $SVR_{12}$.

**History of Diabetes**

Diabetes is an independent risk factor for hepatocellular carcinoma and achieving an SVR may decrease the downstream risk of HCC. Overall, only 7% of Phase 3 study subjects had diabetes at study entry and of these 97% achieved $SVR_{12}$. Again in study M14-002 the addition of RBV and in study M13-099 extending duration of treatment to 24 weeks in GT1a subjects were associated with increased rates of response.

**History of Depression or Bipolar Disorder**

Subjects with significant depression or other psychiatric illnesses are often excluded from peg-IFN therapy as pegIFN can make these illnesses worse. Having depression or another psychiatric illness has not been shown to be an important predictive factor associated with failing to achieve virologic response with DAA regimens. Overall, 9% of subjects enrolled in the Phase 3 trials had a history of depression or bipolar disorder, and 94% achieved $SVR_{12}$. No subjects with a severe psychiatric disorder were enrolled in any of the Phase 3 trials. However, achievement of high SVR rates in a population previously excluded from treatment provides an opportunity that was not otherwise available.

**History of Bleeding Disorders**

Before effective screening of the blood supply and viral inactivation techniques were introduced in the mid 1980's, the population most at risk for getting hepatitis C and other blood-borne viruses, such as HIV and hepatitis B, was largely made up of those with various types of bleeding disorders. Interferon is a known cause of thrombocytopenia, which affects clotting, and ribavirin can cause hemolytic anemia, which affects red blood cell counts. A substantial percentage of patients with bleeding disorders has advanced liver disease, and are most in need of therapy, but they are the worst candidates for current standard therapy, and they are frequently excluded from trials of peg-IFN/RBV-based therapies because of the severity of their condition and risks of toxicities. The advent of interferon-free DAA therapy holds the promise of a greater chance of cure for these patients with manageable adverse events.

A total of 27 subjects with a history of a bleeding disorder were enrolled in the Phase 3 trials and all achieved $SVR_{12}$.

**Former IV Drug Users**

This is an irrelevant population because being a former IV drug user has no bearing on response to treatment with DAAs. Previously there was concern about recidivism among this population when treated with pegIFN, which must be subcutaneously injected. Overall, 97% of former IV drug users achieved an $SVR_{12}$.

***Reviewer comment: A more important population that was not included in the clinical trials were those who are active IV drug users, as this is the currently the highest HCV transmitting population.***

**Baseline Platelet Count (Study M13-099 only)**

In the Compensated Cirrhosis trial, subjects with baseline platelet counts <90 x $10^9$/L achieved higher $SVR_{12}$ rates when treated for 24 weeks: 96% compared to 83% for those treated for 12 weeks. Among subjects with platelet counts ≥90 x $10^9$/L at baseline, the $SVR_{12}$ rates were 93% and 96% in the 12-week and 24-week arms, respectively.

**Baseline Albumin (Study M13-099 only)**

An analysis of subjects with baseline albumin levels <3.5 mg/dL and >3.5 mg/dL was conducted. As with other endpoints, for both subgroups, subjects treated for 24 weeks had improved response rates when treated for 24 weeks: <3.5 mg/dL 84% versus 89%, >3.5 mg/dL 93% versus 97%.

**Baseline Child-Pugh Score (5 versus 6) (Study M13-099 only)**

There were few subjects with Child-Pugh scores ≥6: 38 in the 12 week arm and 32 in the 24 week arm. Overall, subjects with Child-Pugh scores of 5 responded better than those with higher scores (≥6): 95% compared to 88.5%. In general, 24 weeks of treatment appeared to numerically increase $SVR_{12}$ rates among subjects with scores ≥6: 33/38 (87%) with 12-weeks compared to 29/32 (91%) with 24-weeks of treatment.

## 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As described above, the demographic and disease characteristics where generally comparable between non-cirrhotic subjects enrolled in the PBO and Regimen-Controlled trials. As such, the efficacy data were pooled to assist in regimen determination and recommendations.

**Table 21 $SVR_{12}$ rates by regimen and subgroups, non-cirrhotic subjects**

| n/N (%) | 3-DAA + RBV x 12 weeks N=1171 | 3-DAA x 12 weeks N=509 |
|---|---|---|
| GT1a naive | 404/422 (96) | 185/205 (90) |
| GT1a experienced | 166/173 (96) | - |
| -prior null | 83/87 (95) | Not |
| -prior partial | 36/36 (100) | Studied |
| -prior relapse | 47/50 (94) | - |
| GT1b naive | 357/361 (99) | 207/209 (99) |
| GT1b experienced | 204/211 (97) | 91/91 (100) |
| -prior null | 86/90 (95.5) | 32/32 (100) |

| | | |
|---|---|---|
| -prior partial<br>-prior relapse | 52/53 (98)<br>67/68 (98) | 26/26 (100)<br>33/33 (100) |

Two issues related to the proposed recommendations for dosing are worthy of further discussion:

1. Should all GT1a TN subjects be treated with RBV?
2. Should all GT1a cirrhotic subjects be treated for 24 weeks?

The Applicant proposed [redacted] (b) (4)

**GT1a treatment naïve (non-cirrhotic):** The recommended regimen will be 3-DAAs + RBV for 12 weeks. This recommendation is based on:

- The data in GT 1a treatment naïve subjects suggests that RBV is an important component necessary to reduce virologic failure (and presumably treatment-emergent resistance), especially in subjects with non-CC IL28b genotypes.
- No subpopulation was identified that predicted a higher response to treatment without RBV.
- Data included in the 4-month safety update identified three additional late relapses (all with the IL28B CC genotype) among treatment naïve non-cirrhotic GT1a subjects treated with the 3-DAA alone, which further illustrated the added efficacy benefit of including RBV for these subjects, even in those with the favorable IL28B genotype.
- Although the risk of virologic failure is small when RBV is not co-administered, for those subjects who fail and have resistance mutations there are no acceptable retreatment choices, any retreatment regimen would likely involve use of a pegIFN/RBV-based regimen, or the patient would have to delay re-treatment until any resistance associated mutations have reverted back to wild-type, which could take months to years, or until newer agents become available.
- There were more RBV-associated adverse events such as anemia, pruritus and skin rash, and bilirubin elevations; however, these events were generally tolerable and manageable.

**GT1a treatment naïve and experienced (cirrhotic):** The recommended regimen for treatment naïve and experienced GT1a-infected adults with cirrhosis will be 3-DAA + RBV for 24 weeks.

- Extending the duration of 3-DAA + RBV treatment by 12 weeks increased $SVR_{12}$ rates from 92% to 95% (treatment naïve) and 87% to 95% (treatment experienced), and decreased the virologic failure rate by nearly 50% in all subgroups of GT1a-infected subjects.
- Extending treatment was associated with an increase in the frequency of some adverse events (notably fatigue). The majority of adverse events occurred during the first 12 weeks dosing. Adverse events were generally mild to moderate, manageable, and there were no clinically relevant differences in rates of anemia, SAEs or discontinuations due to adverse events.

***Reviewer comment: The dosing recommendation for these two subgroups differs from those proposed by the Applicant; the above recommendations were communicated to the Applicant during the mid-cycle communication and are being negotiated in the labeling.***

The dosing recommendations for all other GT1-infected groups proposed by the Applicant are supported by the FDA review:

**GT1a treatment experienced (non-cirrhotic):** The recommended regimen will be 3-DAA + RBV for 12 weeks. Regimens without RBV were not evaluated in this population due to concerns about risk of virologic failure.

**GT1b treatment naïve and experienced (non-cirrhotic and cirrhotic):** The recommended regimen for non-cirrhotic patients will be 3-DAA x 12 weeks. This recommendation is based on extremely high $SVR_{12}$ rates of 97-100% in subjects treated either with or without RBV. For GT1b-infected patients with cirrhosis, the regimen of 3-DAA + RBV x 12 weeks resulted in similar $SVR_{12}$ rates to those treated for 24 weeks; 98% and 100%, respectively.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Overall, persistence of efficacy among subjects who achieved $SVR_{12}$ appears to be very high.

In Study M11-652, follow-up visits were planned through PTW48. Among subjects treated with any DAA ± RBV combination who achieved $SVR_{12}$, 501/504 (99%) achieved $SVR_{24}$ and 490/494 (99%) achieved $SVR_{48}$. Among 454 subjects in the Phase 3 trials who achieved $SVR_{12}$, and had data at PTW24, 453/454 (99.8%) $SVR_{24}$.

The 4-month safety update report included an updated summary of late virologic relapse observed across all Phase 2 and Phase 3 trials that studied at least 2 of the DAAs included in the 3-DAA combination. Late relapse after achieving $SVR_{12}$ has been rare, and even rarer after achieving $SVR_{24}$. Considering those with available data for analysis, a total of 11/2943 (0.4%) $SVR_{12}$-achieving subjects have experienced confirmed virologic relapse in the $SVR_{24}$ window, and 2/2581(0.08%) subjects have experienced confirmed virologic relapse after achieving $SVR_{24}$.

If considering these late relapses, the SVR and virologic failure rates for the 3-DAA arm in Study M14-002 change to 180/204 (88%) and 19/204 (9%), compared to 96/100 (96%) and 2/100 (2%), respectively, for subjects in the 3-DAA + RBV arm, further illustrating the added efficacy benefit of including RBV for subjects with GT1a. The updated virologic failure rates for subjects with the IL28B CC genotype are now 5/63 (8%) and 0/31 (0%) for the 3-DAA and 3-DAA + RBV arms, respectively, illustrating that RBV provides an efficacy benefit even in subjects with the favorable IL28B genotype.

Some subjects that participated in the Phase 2 and 3 trials enrolled in a dedicated long-term follow-up study to further assess durability of response and rates of liver-related morbidity and mortality.

**Study M13-102: 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** is an ongoing observational follow-up study to assess resistance and durability of response.

- **Objectives**

The objectives are to assess the persistence of specific HCV amino acid variants associated with drug resistance in subjects who experience virologic failure, assess the durability of response for subjects who achieved $SVR_{12}$ with a regimen including an AbbVie DAA, and summarize results of IP-10 (Interferon gamma-induced protein 10), Fibrotest® and Alpha-Fetoprotein tests.

- **Investigational Plan**

Participation was offered to subjects who received ABT-450, ABT-333 or ABT-267 at any dose level in one of 17 prior AbbVie Phase 2 or Phase 3 trials. Enrollment was targeted at 1000 subjects. Subjects are to be followed for a total of 3 years after their last dose of HCV DAA in the parent clinical trial. Non-responder subjects could receive additional therapy for HCV infection while participating in this study. No therapy was provided as part of this study.

Study visits occur at Day 1, Month 3, Month 6, and every 6 months thereafter until the subject has reached 3 years post-DAA therapy. At these visits samples are collected for HCV RNA and possible resistance analyses. Plasma HCV RNA levels were determined using the Roche COBAS® TaqMan® assay v2.0 (LOD=15 IU/mL; LLOQ=25 IU/mL). If a subject's HCV RNA level changed from <LLOQ to ≥LLOQ during the study, confirmatory testing was completed as soon as possible but no later than 2 weeks after the study visit corresponding with the possible HCV RNA relapse.

- **Outcome Measures**

The primary efficacy variable is the percentage of subjects who achieved an $SVR_{12}$ who experience virologic relapse or have new HCV infection at any time up to the last follow-up time point. The Applicant will conduct nucleotide sequence analyses of HCV drug target genes to distinguish between probable relapse versus probably re-infection. Serious adverse event data will also be collected as will assessment of liver-related morbidity and mortality.

- **Results**

The study is ongoing with 176 subjects enrolled and who have been followed for a median duration of follow-up of 553.5 days (range of 84 to 815 days). Of those enrolled, 170 had an $SVR_{12}$ at the end of their prior study.

- One subject died of natural causes >48 weeks after study entry; this subject had undetectable HCV RNA at the time of death
- No subject has experienced late relapse
- No events of liver-related morbidity/mortality have been reported

- There were no safety issues as subjects are not currently being treated

Among the six non-SVR subjects, four underwent resistance testing to evaluate the persistence of mutations. Three subjects were GT1a and one GT1b, three were peg-IFN/RBV non-responders and one treatment naïve, three had on-treatment virologic failure and one relapsed). Mutations primarily in NS3 at the time of treatment failure (Q80K and D168) appear to be retained for a relatively long time (72-96 weeks). One subject with M28T in NS5A retained this mutation, and had the Q30H mutation emerge, at PTW72.

***Reviewer comment: The overall high rate of persistence of virologic response suggests subjects who achieve $SVR_{12}$ will likely maintain virologic suppression for a prolonged duration and may be at a lower risk of liver-related morbidity and mortality; data on these endpoints will be collected at the end of the follow-up period. However, the new information included in the safety update further reinforces the support for recommending all GT1a treatment naïve non-cirrhotic patients receive RBV. Subjects with resistant mutations, primarily in NS5A, will likely have difficulty building an effective regimen as these mutations could persist for upwards of a year.***

### 6.1.10 Additional Efficacy Issues/Analyses

None

# 7 Review of Safety

## ***Safety Summary***

The most important clinically relevant treatment-emergent adverse effect (TEAE) related to treatment with the 3-DAAs was elevated transaminase levels.

ALT elevations were observed in Phase 2 and Phase 3 trials. Treatment with 3-DAA ± RBV generally resulted in a rapid decrease from baseline in ALT levels consistent with the reduction in viral load and hepatic inflammation caused by HCV infection in most patients. Approximately 1% of 3-DAA + RBV-treated subjects experienced a post-baseline ALT elevations of ≥Grade 3. These ALT elevations were generally asymptomatic and occurred during the first 28 days of study drug treatment. There were no Hy's law cases based on review by an independent hepatic expert panel. Most subjects experienced improvement or resolution by the Final Treatment Visit or by PTW 4, and in most cases, the ALT elevation resolved with continued DAA treatment; and, a risk factor of concomitant systemic estrogen-containing medication use was identified ALT elevations.

Transient elevations of total and indirect bilirubin levels are consistent with ABT-450's inhibition of the OATP1B1 transporter. Mean bilirubin levels were higher among subjects treated with 3-DAA + RBV compared to those who did not receive RBV: +1.75 mg/dL and +0.6 mg/dL, respectively. In general, maximum bilirubin increases were observed at Week 1 (day 8), levels either stabilized or decreased during treatment, and were generally at baseline or below baseline levels by PTW 4. For many subjects, the elevated bilirubin value was observed at a single time point. Approximately 2% of study subjects had jaundice or scleral icterus or both.

One subject interrupted DAA treatment for a few days, but no subject discontinued DAAs due to elevated bilirubin levels.

The most important toxicity of ribavirin is hemolytic anemia, which can lead to a ~2 g/dL decrease in hemoglobin levels during treatment. Other adverse events related to treatment with RBV include fatigue, abdominal pain, nausea, pruritus, dyspnea, asthenia, headache, and laboratory events of anemia and hyperbilirubinemia. Also, RBV is a teratogen, and prevention of pregnancy in female subjects and female partners of male subjects is important during treatment and for up to 6-months post treatment. RBV dose modifications due to anemia and other causes did not negatively impact $SVR_{12}$ rates.

Rash and pruritus were reported in subjects treated with 3-DAA, and the frequency of these events was higher in subjects who received RBV. The majority of events was graded as mild or moderate in severity and responded to treatment with topical or oral corticosteroids, oral antihistamines and/or other over-the-counter topical agents. Two subjects had a decrease in RBV dose due to pruritus, but no subject discontinued RBV or interrupted or discontinued the DAAs. There were no SAEs or severe cutaneous reactions, such as SJS, TEN, EM or DRESS.

Common adverse events reported by subjects treated with the 3-DAA + RBV were fatigue, headache, nausea, insomnia, pruritus, diarrhea, asthenia, and rash. When RBV was not included in the regimen, the frequency of nausea, insomnia, pruritus and anemia were decreased. Overall, there were very few laboratory abnormalities observed in the clinical trials.

Two issues related to safety were specifically evaluated: (1) is there a safety consequence to treating all GT1a non-cirrhotic subjects with RBV, and (2) is there a safety consequence to extending the duration of treatment to 24 weeks in all GT1a cirrhotic subjects.

For #1, there were only small numeric increases in the frequencies of most adverse events among subjects who received RBV compared to those who did not receive RBV. For #2, there were no clinically relevant safety differences between cirrhotic subjects treated for 12 or 24 weeks. The majority of TEAEs occurred within the first 85 days of dosing, the mean time to a RBV dose reduction was 37.5 days in the 12-week arm and 43 days in the 24-week arm.

In the liver transplant trial, the type of adverse events that occurred were similar to those observed in the Phase 3 trials, but the frequency was generally higher in transplant recipients. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. A total of 19 subjects (50%) underwent a RBV dose reduction compared to 6% of subjects across the Phase 3 trials; however, RBV dose modification did not impact SVR rates. Five subjects required erythropoietin, and no subject received a blood transfusion.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety analysis was performed on data from the two Phase 2 trials M11-652 and M14-103 and all six Phase 3 trials.

Additional safety data came from the small transplant study, M12-999, in which 34 subjects were treated with 3-DAA + RBV x 24 weeks that was submitted after the NDA was submitted. All analyses are based on subjects who received at least one dose of study medication.

### 7.1.2 Categorization of Adverse Events

Adverse events were defined as any event that began or worsened in severity after treatment was initiated through 30 days after the last dose. Adverse events in the Phase 3 trials were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The disease and demographic characteristics across trials were similar with no clinically relevant differences noted. Based on the ability to pool efficacy data to reach regimen recommendations, it was possible to similarly pool safety data. In general, non-cirrhotic and cirrhotic subjects are discussed separately, and compared as needed.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

When the NDA was submitted, the safety database included 2964 subjects who received at least 1 dose of any combination of the DAAs ± RBV: 643 in the Phase 2 trials M11-652, M14-103, and M12-999, and 2,066 subjects in the Phase 3 trials.

Across the Phase 2 trials, 160 subjects received the 3-DAA + RBV regimen for 12 weeks and 159 for 24 weeks.

In the Phase 3 trials, subjects were treated with the 3-DAAs at the proposed doses for marketing for 12 (1,888) or 24 (172) weeks, and 1,551 with and 509 without RBV. An additional 255 subjects were initially treated with PBO and subsequently treated with 12 weeks of 3-DAA + RBV.

The mean duration of exposure to study drugs among subjects assigned 12 weeks of treatment was 89.6 ±25.30 days, and 164.5 ±19.61 days for those assigned 24 weeks of treatment. Overall, 97% of subjects completed their assigned full course of treatment.

The baseline demographic characteristics of study subjects were generally comparable across treatment groups and trials. Of note, the enrollment of Black/African Americans was very low compared to Whites, despite being over-represented in the general population of HCV infected persons in the United States.

### 7.2.2 Explorations for Dose Response

Greater decreases in viral load from baseline were observed for the higher exposures associated with the 25 mg dose level of ombitasvir compared to a 1.5 mg dose. Doses of ABT-450 <150 mg were associated with lower rates of virologic response and doses ≥200 mg were associated with more frequent ALT and bilirubin elevations. Doses of dasabuvir 800 mg per day were associated with more frequent and greater reductions in hemoglobin levels (see Section 5.3).

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was required or conducted.

### 7.2.4 Routine Clinical Testing

Routine clinical testing for adverse clinical and laboratory events was comprehensive. Adverse events, serious and non-serious, were collected beginning after the informed consent form was signed through the Safety follow-up assessment. Adverse events were recorded regardless of the suspected cause of the event. Study visits occurred at Treatment Weeks 1, 2, 4, 6, 8, 10, and 12, and Post-Treatment Weeks 2, 4, 8, 12, 24, 36, and 48. Unscheduled visits were conducted for premature discontinuation from treatment and as needed to assess progression and/or resolution of events.

Safety evaluations included clinical laboratory assessments, clinical evaluation of vital signs, physical examinations, ECGs, and the subjective reporting of adverse events. For each adverse event, the following information was collected: description, classification of “serious” or “not serious,” date of first occurrence and date of resolution (if applicable), severity, causal relationship (possible, probably or definite), action taken, outcome, and concomitant or other treatment given. Similar requirements were in place for laboratory abnormalities as adverse events. Grading of hematology and clinical chemistry abnormalities were adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Many laboratory parameters were reported in SI units, and these values were converted by this reviewer and presented in US Conventional Units.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Results of the metabolic, clearance and interaction workup are summarized in Section 4.2 above.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Paritaprevir is a protease inhibitor (PI) and there are currently three other PIs approved: boceprevir, telaprevir, and simeprevir. Telaprevir and simeprevir are associated with skin and skin structure reactions. Further, co-administration of boceprevir and telaprevir with pegIFN/RBV leads to high rates of anemia and anemia-related adverse events. Unlike these other PIs, paritaprevir inhibits the OATB1 transporter which results in hyperbilirubinemia

(primarily indirect), and is associated with more frequent elevations in hepatic transaminase levels. Ombitasvir is a NS5A inhibitor, and dasabuvir is a non-nucleoside inhibitor; there are no other drugs in these classes currently approved.

## 7.3 Major Safety Results

The primary paritaprevir safety finding which may pose a clinical risk to patients is alanine aminotransferase (ALT) elevations.

ALT elevations were observed in Phase 2 and Phase 3 trials. Treatment with 3-DAA ± RBV generally resulted in a rapid decrease from baseline in ALT levels consistent with the reduction in viral load and hepatic inflammation caused by HCV infection. Approximately 1% of 3-DAA + RBV-treated subjects experienced a post-baseline ALT elevations of ≥Grade 3. These ALT elevations were generally asymptomatic and occurred during the first 28 days of study drug treatment. There were no Hy's law cases based on review by an independent hepatic expert panel. Most subjects experienced improvement or resolution by the Final Treatment Visit or by PTW 4, and in most cases, the ALT elevation resolved with continued DAA treatment; and, a risk factor of concomitant systemic estrogen-containing medication use was identified ALT elevations.

Pariptaprevir affects the OATB1 transporter, and this led to bilirubin elevations being observed in the clinical trials. Bilirubin was predominantly indirect, it occurred early during treatment (by day 8-15), was generally not associated with signs or symptoms, stabilized and returned to baseline or near baseline levels by end of treatment or PTW4.

The most important RBV-related toxicity is hemolytic anemia; hemolysis may have also contributed to the occurrence of hyperbilirubinemia. Other adverse events related to RBV include fatigue, abdominal pain, nausea, asthenia, insomnia, dyspnea, cough, dry skin, rash and pruritus, and the frequency of these events were higher in subjects treated with RBV.

Of note, paritaprevir was shown in preclinical animal studies to cause gall bladder erosions, and there were five subjects with SAEs related to gall bladder disease. It was not possible to rule out a relationship between these events and the DAAs, and post-marketing surveillance for these types of events is recommended.

### 7.3.1 Deaths

A total of seven deaths were included in the safety database; six occurred in the post-dosing follow-up period and were due to reasons not related to study drugs (non-small cell lung cancer, arteriosclerosis, coronary artery stenosis and arteriosclerosis, left frontal parenchymal hematoma after cardiac catheterization, *Stenotrophomonas* infection, *Escherichia* sepsis, *Candida* sepsis, and aspergillosis, and found dead (asystole)). There was one on-treatment death, which is described herein:

- In Study M13-099, subject 382123 was a 64 year old female randomized to 3-DAA + RBV x 12 weeks. The subject had a history of cirrhosis, Childs-Pugh score of 5, diabetes mellitus, and had been taking metformin and Januvia since 1988. At screening her metformin dose was increased from 1000 mg BID to 1000 mg TID and she received

furosemide and spironolactone for an unknown reason. On day 1 she had peripheral edema of unknown etiology. On day 2 was hospitalized and her diuretics were increased. On day 7 she experienced nausea and vomiting and was treated with gaviscon. On day 8 she discontinued all study medications. On day 10, she experienced lactic acidosis that required hemodialysis. On day 12 she experienced multi-organ failure with rhabdomyolysis. On day 13 she underwent a liver transplant. Following the transplant, the lactic acidosis, rhabdomyolysis and multi-organ failure resolved. On day 94 the patient died (81 days post liver transplant); the preliminary cause of death was renal failure with bleeding complications. An evaluation of the explant showed necrosis of hepatic parenchyma, preexisting cirrhosis, probably steatosis, mainly macrovacuolar estimated between 30-50%, and it was difficult to estimate existence and extent of potential microvacuolar steatosis due to massive necrosis of parenchyma. The investigator assessed the events of lactic acidosis, nausea and vomiting as possibly related to study medication; the Applicant assessed all events as not related to study medications and more likely related to metformin use in a subject with cirrhosis. The dose of metformin was not increased by the investigator and the Applicant was unable to determine the reason.

According to the Applicant, the metformin dose increase may have initiated a cascade of events that led to this subject's demise. Metformin-associated lactic acidosis (MALA) can occur in patients with shock or tissue hypoxia, or in the presence of impaired renal function, advanced liver disease or decreased tissue perfusion and can become self-perpetuating unless it is identified and corrected, leading to shock and multi-organ system failure. Further, the subject underwent aggressive diuresis and antihypertensive use that could have compounded MALA. The subject had shock liver (sudden rise in transaminase levels) associated with rise in lactate dehydrogenase, which led to multi-organ failure.

The explant was evaluated by Dr. Zach Goodman, who is a well-known hepatic pathologist. According to Dr. Goodman, the histologic findings are consistent with severe ischemic-hypoxic hepatic necrosis in a patient with underlying cirrhosis and steatosis, and the findings do not suggest a drug-induced or toxic liver injury.

Reasons cited by the Applicant that suggest the DAAs were not contributory include:

- Preclinical studies of paritaprevir/ritonavir, ombitasvir and dasabuvir showed no evidence of lactic acidosis or widened anion gap
- Histologic examination from preclinical studies shows no evidence of mitochondrial toxicity
- Paritaprevir, ritonavir, ombitasvir and dasabuvir are unlikely to affect metformin exposures, as none of the compounds are expected to have any impact on renal transporters involved in the elimination of metformin
- Serum ALT values during DAA + RBV treatment do not suggest drug induced liver injury and liver histology was consistent with severe ischemic hypoxic necrosis and not drug-induced or toxic liver injury

- Liver histology did not suggest drug induced liver injury (DILI) or toxic liver injury
- The DSMB determined that the events were related to metformin and not to DILI
- Thirty-two subjects used metformin as concomitant medication and no other subject experienced a similar event

***Reviewer comment: The metformin label warns against patients with advanced liver disease (including liver failure and cirrhosis) taking metformin as they can be at an increased risk of lactic acidosis. The Applicant was unable to determine why the subject had her metformin dose increased at study entry. Based on review of this case, it is likely that mismanagement of metformin in a patient with high risk of complications was the primary reason for this subject's rapid deterioration, need for a liver transplant, and subsequent death.***

### 7.3.2 Nonfatal Serious Adverse Events

The frequency of nonfatal SAEs was low among subjects treated with the 3-DAA ± RBV regimens: 3%. Treatment-emergent events probably related to the DAA and/or RBV included acute cholecystitis, anemia, and arthralgia.

In preclinical animal studies, paritaprevir caused gall bladder erosions, and there were five subjects with SAEs related to gall bladder disease. Of these subjects, 4/5 had a history of gall bladder disease prior to study entry, 1/5 had significantly elevated LFTs at the time of cholecystitis, 2/5 interrupted study drugs, and all five achieved $SVR_{12}$.

- **Phase 2 Trials**

Twelve of 643 subjects (2%) in the Phase 2 trials M11-652, M14-103 and M12-999 experienced SAEs; eight were treatment-emergent and four occurred in the post-treatment follow-up period. One treatment-emergent event of arthralgia and one early post-treatment event of cholecystits were possibly related to study drugs.

- Subject 8231 was a 52 year old male with a history of cholecystitis in 2009. On day 190 (22 days after completing treatment), he complained of RUQ pain. Abdominal ultrasound showed cholelithiasis with gall bladder wall thickening. On day 193 he underwent a laparascopic cholecystectomy and recovered without sequelae.

- Subject 5761 was a 26 year old female. On day 8 she complained of bilateral knee pain which progressed in severity; the pain resolved on study day 29 without sequelae. No etiology for her arthralgia was identified.

Not related treatment-emergent events included: facial paresis (likely associated with herpes), bronchitis (due to a respiratory tract infection) with blood creatinine increased (likely due to concomitant medications), animal bite, affective disorder (likely due to deterioration of baseline bipolar disorder), hypotension and tachycardia following carotid endarterectomy, peripheral edema in a diabetic subject, and pneumonia. Post-treatment events were: CVA likely due to sarcoma, acute myeloid leukemia (subject complained of bruising, low platelet count, and blurred vision), neck pain with cervicobrachial syndrome.

- **Phase 3 Trials**

Three percent of subjects (78/2321) in the Phase 3 trials experienced non-fatal SAEs.

Of note, four subjects had treatment-emergent gall bladder-related SAEs: acalculous cholecystitis, cholecystitis (2), and acute biliary colic with duct stone. Paritaprevir caused gall bladder erosions and gall bladder wall thickening in pre-clinical studies, and it interferes with one of the bilirubin transporters. Therefore, it was not possible to rule out a relationship between these events and the DAAs.

In addition to gall bladder-related events, 19 subjects had events where either the Investigator or Applicant determined there was a reasonable possibility of relatedness to the 3-DAA and/or RBV were: anemia (3), possible exacerbation of coronary artery disease with anemia (1), anemia with shortness of breath (1), acute respiratory failure (2), acute renal failure (1), acute hepatitis with concomitant estrogen use (1), pruritus/angioedema (1), abdominal pain/dizziness/nausea/vomiting (2), arthralgia (1), cellulitis (1), and cerebral vascular accident (1) (see Table 22).

**Table 22 SAEs possibly related to study drugs in Phase 3 trials**

| Study | ID | Age/ Sex | Regimen | Summary of Event(s) | Comments |
|---|---|---|---|---|---|
| M11-646 | 128204 | 58 ♂ | 3-DAA + RBV | Day 60: anemia (Hgb 8.9 mg/dL), bilirubin 1.9 mg/dL, with non-cardiac chest pain, dyspnea and cough | Probably related to RBV. RBV discontinued, no change to 3-DAA. Hgb levels normalized by end of treatment period (12 mg/dL). All events resolved without sequelae. |
| M11-646 | 128208 | 36 ♂ | 3-DAA + RBV | Day 69: grade 3 abdominal pain, nausea and vomiting<br>Day 81: acalculous cholecystitis with biliary sludge (no stones); bilirubin normal. Study drugs interrupted for 2 days. Underwent cholecystectomy and recovered without sequelae | Subject had no prior history of gall bladder disease<br><br>Event assessed as not related to study drugs |
| M11-646 | 383207 | 56 ♂ | 3-DAA + RBV | Day 7: headache<br>Day 12: worsening headache with photophobia. Oxygen saturation 97%, study drugs interrupted. Day 13: oxygen saturation 88% on 6 L/min oxygen. Dyspnea and polypnea. CXR showed left pneumopathy. Subject was intubated and ventilated.<br>Day 20: improvement noted and ventilator removed.<br>Microbiologic samples negative.<br>Treated with Tavanic, Zithromax, Augmentin and Rocephin.<br>Day 26: discharged.<br>Day 31: events resolved | No alternative etiology identified<br><br>Study drugs could not be restarted because duration of interruption >7 days |
| M11-646 | 420203 | 66 ♀ | 3-DAA + RBV | Day 26 of OL treatment: Grade 4 severe biliary colic, cholecystitis. Study drugs interrupted for 5 days. Underwent | Subject had history of cholelithiasis<br>Event assessed as not |

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| | | | | cholecystectomy and recovered without sequelae | related to study drugs and more likely related to underlying condition |
| M11-646 | 803211 | 46 ♀ | 3-DAA + RBV | Day 1: Severe cramping abdominal pain, nausea and dizziness while driving home 30 minutes after ingestion of the first dose of study drugs. Forty-five minutes after ingestion she vomited several times and had uncontrolled massive bowel movements. The subject's husband called an ambulance. She was found to be hypotensive (90 mmHg), hypothermic (35.5 C) and slightly hyporesponsive. After receiving IV fluids, her blood pressure normalized. Her complaint of nausea improved with Metoclopramide. She was found to have sinus tachycardia with ventricular extrasystole in bigeminy.<br>Day 2: events resolved and she was discharged. | Study drugs were discontinued and not restarted because the subject felt she would not be able to tolerate the nausea and the investigator was unsure whether more serious cardiac arrhythmia could develop with a second medication challenge. |
| M13-098 | 109311 | 58 ♀ | 3-DAAs + RBV | Day 1 of OL treatment: prutitus.<br>Day 12: angioedema with swelling to left side of mouth and lip. Admitted to hospital and treated with diphenhydramine and methylprednisolone; event resolved same day. | Study drugs discontinued<br>Subject was taking the ACE inhibitor, lisinopril, which can cause drug-induced angioedema.<br>Applicant: temporal plausibility for an association. Angioedema previously noted to occur with both ribavirin and ritonavir |
| M13-098 | 128304 | 50 ♀ | 3-DAAs + RBV | Day 70: dizziness, nausea, vomiting with marked bradycardia, incomplete RBBB. Subject hospitalized. | Study drugs interrupted and restarted without repeat episode<br>Assess as possibly due to viral illness although no workup. Subject had a past history of bradycardia; ECG similar to one performed 2 years prior |
| M13-098 | 380301 | 63 ♂ | 3-DAAs + RBV | Day 54: acute transient cerebral attack/stroke that regressed within 1 hour.<br>Day 55: admitted to the Stroke Unit. Examination and CT scan normal. Cardiac ultrasound demonstrated intra-auricular communication with a shunt. Subject put on acetylsalicylic acid to prevent recurrence.<br>Day 59: the event resolved, and the subject was discharged without recurrence. | No change in study drugs<br>Investigator: reasonable possibility as alternative etiology was not identified.<br>Applicant: no reasonable possibility; more likely related to another factor such as the patient's chronic hypertension, an embolus or ASD with shunt. |
| M13-098 | 400305 | 57 ♀ | 3-DAA + RBV | Day 28 of OL treatment: acute biliary colic with duct stones. ALT 260 U/L. AST 309 U/L and bilirubin 259 mcmol/L. Subject underwent ERCP on day 29 | No change in study drugs<br>Subject had past history of cholelithiasis.<br>Assessed as not related |

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| | | | | and then a post treatment cholecystectomy. ALT, AST and bilirubin normalized. | to study drugs |
| M13-098 | 563306 | 68 ♀ | 3-DAA + RBV | Day 1: malaise, shivering, fatigue, weakness, constipation and nausea.<br>Day 2: oliguria with edema in lower extremities.<br>Day 3: acute renal failure (Cr 1.2 mg/dL, urea 55 mg/dL)<br>Day 5: renal failure resolved and subject was discharged | Study drugs discontinued<br><br>Investigator: likely due to RBV<br><br>Applicant: likely due to dehydration |
| M13-961 | 100505 | 62 ♂ | 3-DAA + RBV | Day 27: chest pain with shortness of breath, Hgb 9.3 mg/dL<br>Day 28: echo showed normal wall motion with ejection fraction of 50-55%, stress test positive for pain and ST depression.<br>Day 29: DAA/RBV interrupted Hgb 9.4 mg/dL. Angiogram showed 3-vessel disease and subject underwent CABG<br>Day 30: DAA restarted, Hgb 9.4 mg/dL<br>Day 31-35: DAA interrupted, Hgb 7.6 mg/dL<br>Day 36: DAA and RBV restarted at 400 mg QD, Hgb 10.7 mg/dL<br>Day 52: RBV increased to 600 mg QD, Hgb 11.3 mg/dL | Assessed as not related to study drugs.<br><br>Subject had a history of hypertension, hypercholesterolemia, and edema in lower extremities. |
| M13-961 | 237513 | 48 ♀ | 3-DAA | Day 73: hospitalized due to "arthralgia and swelling of the palm joints and foot joints" that was severe in intensity. She was diagnosed with non-differentiated arthritis. Laboratory evaluation included C-reactive protein of 66.3 mg/dL, Hgb 11.5 g/dL, uric acid 9.3 mg/dL, and ESR of 38 mm/hr (normal ranges not provided). She was treated with methotrexate, Voltaren and nimesulide. | No change in study drugs<br><br>Possibly related as no alternative etiology for the arthralgia/arthritis was identified |
| M14-002 | 101410 | 65 ♀ | 3-DAA + RBV | Day 35: presented with tiredness and Hgb of 7.8 mg/dL.<br>Day 41: blood transfusion, Hgb increased to 9.7 mg/dL<br>Day 116: Hgb 13.4 mg/dL. | RBV interrupted days 47-52 and 77-85<br><br>No change in DAA dosing<br><br>Assessed as related to RBV |
| M13-099 | 137103 | 61 ♀ | 3-DAA + RBV x 24 weeks | Day 1: anxiety<br>Day 2: difficulty sleeping<br>Day 3: lower extremity edema, decreased appetite, myalgias, pruritus and worsening heartburn, and fatigue beginning study day 5 that improved. Wheezing beginning day 8 and on day 12 and found to have abnormal pulmonary findings, non-productive cough, runny nose, and worsening abdominal swelling.<br>Day 4: respiratory distress, fever, tachypnea, hypoxia, diffuse wheezing, upper respiratory stridor, diffuse | Study drugs discontinued<br><br>Investigator: possibly related to study drugs<br><br>Applicant: not related due to a combination of newly diagnosed COPD due to prior smoking history and the concurrence of a rhinovirus respiratory tract infection |

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| | | | | bilateral interstitial infiltrates and elevated WBC with lymphocytosis, and was admitted to the ICU for respiratory distress with a leading diagnosis of bilateral interstitial pneumonia with systemic inflammatory response. On hospitalization day 3, her respiratory status continued to improve. She was transferred out of the ICU to the general medicine floor. Supplemental oxygen requirement was lessened to 2 liters by nasal cannula. She was found to have a positive culture for Rhinovirus. On study day 18, the patient was discharged from the hospital.<br>Day 42: intracranial aneurysm | |
| M13-099 | 119103 | 58 ♀ | 3-DAA + RBV X 12 weeks | Day 16: presented with acute RUQ pain. Abdominal ultrasound showed cholelithiasis with dilated common bile duct. Bilirubin 12 mcmol/L, other LFTs WNL. Study drugs interrupted x 5 days. Day 19 subject underwent cholecystectomy and recovered without sequelae. | Subject had history of cholecystitis/cholelithiasis<br><br>Event assessed as not related to study drugs |
| M13-099 | 111109 | 25 ♀ | 3-DAA + RBV x 12 weeks | Day 8: acute hepatitis (ALT 233 U/L, total bilirubin 3.7 mg/dL, direct bilirubin 1.4 g/dL,). Study drugs discontinued day 10 (ALT 497 U/L, total bilirubin 4.3 mg/dL, direct bilirubin 2.06 g/dL). ALT continued to increase for two days with a peak off-treatment level of 819 U/L; bilirubin levels began and continued to decrease. ALT and bilirubin levels continued to decrease and the last ALT value was 100 U/L. There were no changes in alkaline phosphatase levels or coagulation parameters. | Subject was taking oral contraceptive Orsythia.<br><br>Probably due to interaction between ABT-450 and OC |
| M13-099 | 116104 | 67 ♀ | 3-DAA + RBV x 24 weeks | Day 7: Hgb 11.2 mg/dL (baseline 11.7 mg/dL) which remained stable through Week 16. The anemia worsened between Week 16 (Hgb 11.6 mg/dL) and Week 20 (Hgb 10.2m g/dL). Following the Week 20 visit, subject developed worsening shortness of breath and hospitalized (Hgb 7.2 mg/dL). She discontinued study medications and shortness of breath and anemia resolved. | DAA and RBV discontinued<br><br>Probably related to prolonged RBV-induced anemia |
| M13-099 | 403101 | 53 ♂ | 3-DAA + RBV x 24 weeks | Day 156: presented with cellulitis on both feet that were severe in intensity. The subject was hospitalized; a wound culture was positive for Escherichia coli. The subject was treated with ampicillin/clavulanate. Subject had a history of diabetes. | No change in study drugs<br><br>Assessed as possibly related to DAA |
| M13-099 | 380111 | 58 ♂ | 3-DAA + RBV x 12 weeks | Week 4: anemia (Hgb 11.7 mg/dL), which worsened on treatment and at week 10 the subject underwent RBV dose reduction (Hgb 8.4 mg/dL). The | Study drugs discontinued<br><br>Assessed as related to RBV |

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| | | | | anemia continued to worsen and at week 12 the subject was hospitalized and received a blood transfusion (Hgb 7.8 mg/dL). Following the transfusion and RBV dose reduction, the anemia resolved. | |

Based on a review of narratives of other SAEs, events determined not related to study drugs either due to subject history, pathophysiology, or timing (e.g., occurred prior to dosing or well after dosing was completed). In general, there were no patterns to these other events which included: mediastinal mass/NSCLC, acute appendicitis (2, one started prior to DAA dosing), overdose/suicide attempt, aortic occlusion/post-operative wound infection, anaphylaxis due to a sting, lobar pneumonia, diarrhea, antidepressant addiction, lumbar fracture following bike accident, epidermal abscess, tendon disorder, tibia/fibula fracture, epididymitis, atrial fibrillation with hypokalemia (negative re-challenge), Brugada syndrome, uterine polyp, coronary artery disease (2), small bowel obstruction (2), head trauma/broken clavicle secondary to a motorcycle accident, cellulitis following trauma, vasovagal episode secondary to a blood draw, a femoral neck fracture, extradural hematoma secondary to a fall, URI/pharyngitis, delirium, shoulder tendonitis, ureteral colic, nephrolithiasis (2), abdominal pain, increased glucose, exacerbation of osteoarthritis (2), groin abscess, bleeding esophageal varicies, head injury secondary to a fall, ductal carcinoma in situ of right breast, myalgia secondary to excessive physical work (negative re-challenge) and two subjects diagnosed with HCC.

In addition, the extended duration of treatment in the Compensated Cirrhosis trial did not appear to substantially increase the occurrence of SAEs: 11/13 (85%) SAEs in the 12-week arm occurred between days 1-85 and 2/13 (15%) occurred during post-treatment follow-up while 3/7 (43%) in the 24-week arm occurred between days 1-85, 2/7 (28.5%) between days 86-167, and 2/7 (28.5%) occurring in the post-treatment follow-up period.

Of note, one subject each experienced a syncopal episode and atrial fibrillation while receiving PBO during DB treatment.

### 7.3.3 Dropouts and/or Discontinuations

Dropouts and discontinuations due to adverse events occurred in ~1% of subjects treated with the 3-DAA. Events of anemia and cholecystitis were the two most frequently cited reasons for study drug discontinuation. Although more subjects discontinued from the Compensated Cirrhosis trial, there was no pattern to the events or increase in frequency of events compared to non-cirrhotic subjects.

- **Phase 2**

Twelve of 643 subjects (2%) prematurely discontinued study drugs due to an adverse event.

In Study M11-652, nine subjects prematurely discontinued study drugs due to anemia/decreased hemoglobin levels (2), affective disorder (1; also SAE), homicidal ideation (1), convulsions (1), cholestatic hepatitis (1), anxiety (1), asthenia with jitteriness and confusional state (1), and, headache, constipation, nausea, diarrhea, aphthous stomatitis, generalized pruritus and burning sensation (1). The following five subjects discontinued due to events where a causal relationship to the DAAs/RBV could not be ruled out.

- Subject 5255 was a 37 year old male in Group A (3-DAA + RBV x 8 weeks) with a history of bipolar disorder, depression, anxiety who was taking lithium prior to study entry. On day 27 he reported headache, and on day 32 photophobia with hyperhidrosis and altered mood. His lithium was discontinued on day 35 and he had a convulsion on day 51. The study drugs were discontinued on day 52. This subject had no prior seizure history and the Investigator suspected the convulsion was due to abrupt discontinuation of lithium.

**Reviewer comment: Lithium is metabolized by CYP3A4 and concentrations would be expected to increase with co-administration of RTV. Two side effects of elevated lithium levels are headache and hyperhidrosis, and convulsions/seizures are a symptom of lithium overdose. The seizure in this subject may have been related to an interaction between the DAA and lithium and the pattern appears possibly indicative of lithium toxicity.**

- Subject 5401 was a 41 year old black male in Group F (ABT-450/r + ABT-267 + ABT-333 + RBV x 12 weeks). On day 43, subject had a hemoglobin level of 9.1 mg/dL. On day 46 study drugs were discontinued. On day 68 the hemoglobin level was 10.8 mg/dL.

- Subject 8014 was a 58 year old white female in Group M (ABT-450/r + ABT-267 + ABT-333 + RBV x 24 weeks). On day 72 the subject reported nausea. On day 87 she experienced decreased creatinine clearance (39 mL/min) and hemoglobin level (8.2 mg/dL) and discontinued study drugs. The event of creatinine clearance decrease resolved on day 114 and the event of hemoglobin decrease was ongoing.

**Reviewer comment: Two events of discontinuation due to anemia, one with associated renal insufficiency, which were likely due to RBV.**

- Subject 5118 was a 48 year old male in Group F (3-DAA x 12 weeks). On day 61 he was diagnosed with cholestatic hepatitis and on day 63 he discontinued all study medications. Relevant labs showed ALT 162 U/L, AST 74 U/L, total bilirubin 4.3 mg/dl, indirect bilirubin 2.3 mg/dl, alkaline phosphatase 99 U/L, and GGT 223 U/L. Abdominal ultrasound showed gallstones near the gallbladder neck. On day 78 the event was considered resolved.

**Reviewer comment: A causal relationship between ABT-450 and transaminitis could not be ruled out in this subject.**

- Subject 8169 was a 58 year old white female in Group J (ABT-450/r/ABT-267 + RBV x 12 weeks). On day 1 she experienced headache. On day 2 she experienced constipation. On day 34 she experienced nausea. On day 46 she experienced diarrhea. On day 49 she experienced aphthous stomatitis. On day 57 she experienced burning sensation and pruritus. On day 70 study drugs were discontinued. All events were self-limited and resolved without sequelae. The Investigator considered all the events as possibly related to study drugs.

**Reviewer comment: Agree with assessment.**

One subject in Study M14-103 prematurely discontinued study drugs due to an unrelated CVA likely due to a sarcoma. One subject discontinued study drug in Study M12-999 due to possibly related adverse events of memory impairment, rash and anxiety.

- **Phase 3**

Approximately 1% of subjects discontinued study drugs due to adverse events. Events where the relatedness of the event to the DAA and/or RBV could not be ruled out are listed in Table 23, Nine subjects whose events led to premature discontinuation were classified as serious.

In the Compensated Cirrhosis trial, four subjects discontinued from the 12 week arm and nine from the 24 week arm due to adverse events. Of the nine who discontinued from the 24 week arm, four were during the initial 12 weeks and five were during the second 12 weeks of dosing.

Treatment-emergent events not likely related to DAA and/or RBV included events of: pneumonia (2), hepatocellular carcinoma (2), and single events of head trauma following a fall, fractured femur, atrial fibrillation, pneumonia, major depression, pancreatitis, exacerbation of osteoarthritis, increased glucose, bleeding esophageal varicies, pharyngitis, drug toxicity/abuse, and diverticulitis in a subject treated with the 3-DAA.

**Table 23 Discontinuations due to adverse events, Phase 3 trials**

| Study | ID | Age/sex | Regimen | Event(s) | Comments |
|---|---|---|---|---|---|
| M11-646 | 108207 | 49 ♂ | 3-DAA + RBV | Day 1 OL treatment: palpitations | Possibly related to DAA and RBV |
| M11-646 | 803211 | 46 ♀ | 3-DAA + RBV | Day 2 DB treatment: extrasystole ventricular bigeminy, abdominal cramps, diarrhea, shivering, nausea and vomiting, and sinus tachycardia | SAE<br><br>Possibly related to DAA and RBV |
| M11-646 | 118202 | 55 ♀ | 3-DAA + RBV | Day 10 OL treatment: malaise, dyspnea on exertion, palpitations, anxiety, limb parasthesia, chest pressure and syncopal episode | Possibly related to DAA and RBV |
| M11-646 | 120211 | 55 ♀ | 3-DAA + RBV | Day 74 DB treatment: nausea, vomiting, anorexia and fever; lobar pneumonia on CT | SAE<br><br>Probably not related |
| M11-646 | 383207 | 56 ♂ | 3-DAA + RBV | Day 7 of DB treatment: headaches, fever, and dyspnea. Subject admitted to hospital with acute respiratory failure and treated with oxygen and study drugs were interrupted. On day 18 he had a pleural effusion drained. On day 20 he was improved and was discharged on day 26. No bacterial etiology was identified | SAE<br><br>Possibly related to DAA and RBV<br><br>DAAs interrupted for >7 days and could not be restarted per protocol |
| M11-646 | 700206 | 53 ♂ | 3-DAA + RBV | Day 51 OL treatment: agitation | Possibly related to DAA and RBV |
| M13-098 | 361301 | 60 ♀ | 3-DAA + RBV | Day 1 DB treatment: diarrhea, treated with idoform and plantago ovate | Possibly related to DAA and RBV<br>Resolved 11 days after DAA discontinued |

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| M13-098 | 782303 | 58 ♂ | 3-DAA + RBV | Day 14 DB treatment: Grade 3 ALT (297 U/L); day 21 437 U/L. Baseline bilirubin 1.0 mg/dl, increased to 5.0 mg/dl on day 8. Nausea days 3-16, jaundice days 6-18 and asthenia day 7 | Possibly related to DAA, and not related to RBV<br><br>Reviewed by Expert Hepatic Panel |
| M13-098 | 109311 | 58 ♀ | 3-DAA + RBV | Day 1 OL treatment: generalized pruritis, day 12 angioedema left side of mouth and lip; admitted to hospital and treated with diphenhydramine and methylprednisolone; event resolved same day | SAE<br><br>Possibly related to study drugs |
| M13-098 | 563306 | 68 ♀ | 3-DAA + RBV | Day 1 DB treatment: malaise, shivering, vomiting, fatigue, weakness, nausea<br>Day 3: admitted with acute renal failure (Cr 1.2 mg/dL, BUN 55 mg/dL and negative urinalysis); event resolved and discharged day 5 | SAE<br><br>Possibly related to RBV or dehydration |
| M13-099 | 114106 | 64 ♀ | 3-DAA + RBV X 12 weeks | Day 10: altered mental status | Possibly related to interaction between DAA and Wellbutrin |
| M13-099 | 116104 | 67 ♀ | 3-DAA + RBV X 24 weeks | Day 152: anemia | SAE<br>Probably related to RBV |
| M13-099 | 137103 | 61 ♀ | 3-DAA + RBV x 24 weeks | Day 12: exacerbation of COPD | SAE<br>Possibly related to DAA and RBV |
| M13-099 | 206103 | 62 ♀ | 3-DAA + RBV x 24 weeks | Day 99: dysphagia, increased gag reflex, asthenia | Possibly related to DAA and RBV |
| M13-099 | 382123 | 64 ♀ | 3-DAA + RBV X 12 weeks | Day 5: nausea and vomiting | SAE<br>Possibly related to DAA, not related to RBV |
| M13-099 | 111109 | 25 ♀ | 3-DAA + RBV X 12 weeks | Day 8: elevated ALT and bilirubin while taking estrogen-containing OC Orsythia | SAE<br>Probably related to ABT-450 and OC interaction |
| M13-099 | 609102 | 51 ♂ | 3-DAA + RBV X 24 weeks | Day 153: suicidal ideation | Possibly related to DAA, not related to RBV |
| M13-389 | 10303 | 63 ♂ | 3-DAA + RBV | Day 36: anxiety, dyspnea, pyrexia, tachycardia | Possibly related to DAA and RBV |

An assessment of the differences in discontinuations due to adverse events in the Compensated Cirrhosis trial showed that extending duration of treatment did not substantially increase risk. In the 12-week arm, 4 subjects prematurely discontinued due to acute hepatitis, mental status changes, extradural hematoma and MALA. In the 24-week arm, four subjects discontinued, one during the first 12 weeks of dosing due to exacerbation of COPD and three during treatment days 86-167 due to anemia, altered mood/suicidal ideation and dysphagia/asthenia/tremor/dizziness and dehydration.

## 7.3.4 Significant Adverse Events

**Significant Events**

Severe events in Phase 2 trials included a case of muscle spasms due to a concomitant medication (torsemide) and worsening proteinuria (3+ at baseline that increased to 4+ on-treatment and improved to 2+ by end of treatment).

Among non-cirrhotic subjects in the Phase 3 trials treated with the 3-DAA+ RBV, ~14% of subjects experienced a moderate or severe treatment-emergent adverse event. Events that occurred in ≥2% of subjects included fatigue (5%), headache (5%), asthenia (3%), nausea (3%). anemia (2%), insomnia, (2%), and diarrhea (2%). Among subjects treated with the 3-DAA alone, only fatigue (4.5%) and headache (4%) occurred in ≥2%.

In the Compensated Cirrhosis trial, 97 (47%) and 87 (51%) of subjects in the 12- and 24-week arms, respectively, had moderate (9%) or severe (7%) adverse events. Moderate or severe events reported by ≥2% of study subjects in the two arms included: fatigue (7% versus 8%), headache (5% versus 8%), nausea (3% versus 2%), asthenia (2% versus 6%), anemia (3% versus 7%), diarrhea (3% versus 5%), vomiting (<1% versus 2%), asthenia (2% versus 6%), pruritus (3% versus 5%), rash (1% versus 6%), increased bilirubin (8% versus 3%), arthralgia (2% versus 1%), anxiety (2% versus 4%), depression (2% versus 3.5%), insomnia (3% versus 5%), muscle spasms (1% versus 3%), and peripheral edema (1% versus 3.5%). In the 24 week arm, in addition to those already listed, diarrhea and insomnia also occurred in ≥3% of study subjects.

There were four subjects in the Compensated Cirrhosis trial that experienced hepatic decompensation, two in each arm. In the 12 week arm the events leading to a change in classification from Childs-Pugh A to Childs-Pugh B were persistently increased bilirubin and hepatic encephalopathy. In the 24 week arm, the events were jaundice/ascities/bacterial peritonitis and hematemesis/melena/esophageal varicies.

**Adverse Events Leading to Study Drug Interruption**

Approximately 1% of subjects in the Phase 2 and 3 trials temporarily interrupted study drugs due to adverse events. Among subjects who received 3-DAA + RBV the events causing an interruption were: increased bilirubin (2), jaundice (1), increased ALT (4), acute cholecystitis/biliary colic (3), anemia (3), intestinal obstruction (2), nephrolithiasis (1), ureteral calculi (1), altered mental status (1), anxiety (1), asthenia (1), asthenia/diarrhea/fall (1), head trauma (1), dizziness/nausea/vomiting/bradycardia (1), vomiting/diarrhea (1), encephalopathy secondary to attempted suicide/benzodiazepine overdose (1), exacerbation of coronary artery disease (1), atrial fibrillation (1), decreased weight/dehydration (1), and dog bite (1). Among subjects treated with 3-DAA alone, study drugs were interrupted due to one event of heroin abuse and one event of myalgia.

The subjects with heroin abuse, mental status changes, and asthenia also discontinued study drugs. Of the other 28 subjects, interruptions were generally for short durations and all subjects achieved an $SVR_{12}$.

**Adverse Events Leading to Ribavirin Dose Modification**

Overall, 6% of subjects in the Phase 2 and 3 trials underwent a RBV dose modification due to adverse events. Undergoing a RBV dose modification did not negatively impact achievement of SVR.

In Phase 2 trials M11-652 and M14-103, the dose of RBV was modified due to anemia/decreased hemoglobin in 13, subjects and in individual subjects with anemia plus dyspnea or fatigue, pruritus, insomnia, dizziness with cough, wheezing and diarrhea. A higher proportion of subjects in the liver transplant study (M12-999) required a modification of their RBV dose (19/34, 56%). Subjects underwent RBV dose modifications for: 10 due to anemia/decreased hemoglobin, one due to increased creatinine, and nine due to "investigator discretion. One additional subject interrupted RBV for a short duration. All of these subjects achieved $SVR_{12}$.

In the Phase 3 PBO- and Regimen-Controlled trials, 79/1171 subjects (7%) treated with 3-DAA + RBV underwent RBV dose modifications due to adverse events. Reasons for RBV dose modifications in subjects treated with 3-DAA + RBV included: anemia/decreased hemoglobin (55), anemia with other symptoms, such as pallor, fatigue, coronary artery disease, non-cardiac chest pain, dyspnea, dizziness, decreased creatinine clearance, or asthenia (9), fatigue (2), vomiting (2), mental fogginess/irritability (1), insomnia (1), fatigue/dyspnea (1), nausea/headache/dizziness (1), nausea/headache/fatigue/memory loss (1), gastroenteritis (1), increased weight (1), increased bilirubin (1), dyspnea on exertion (1), anxiety (1), and palpitations/cough/dyspnea (1). A single subject in a 3-DAA group had a modification of RBV placebo due to an upper respiratory tract infection/anxiety.

In the Compensated Cirrhosis trial, 39 subjects underwent a RBV modification due to adverse events: 17/208 (8%) subjects in the 12-week arm and 22/172 (13%) subjects in the 24-week arm. Equal proportions of subjects in the 12-week and 24-week arms underwent a RBV dose modification due to anemia/decreased hemoglobin alone or with other symptoms such as dyspnea, fatigue, asthenia, or increased bilirubin: 88% (15/17) and 86% (19/22), respectively. Other events in the 12-week arm were two subjects with increased bilirubin, and in the 24-week arm one event each of increased bilirubin, increased weight, and weight loss.

Of the subjects that underwent a RBV dose modification for any reason in the Phase 3 trials, 98.5% achieved $SVR_{12}$.

## 7.3.5 Submission Specific Primary Safety Concerns

Across the development program, events of special interest of elevations of hepatic transaminase levels (ALT and AST), hyperbilirubinemia (primarily indirect), anemia, and skin and skin structure events have been observed, and are discussed in more detail herein.

**Liver Function Abnormalities/Heptatoxicity**

Among non-cirrhotic subjects, the mean baseline ALT was 66.3 U/L and in cirrhotic subjects it was 99.5 U/L. Treatment with 3-DAA ± RBV resulted in a rapid decrease from baseline in mean ALT levels which is consistent with reduction in viral load and hepatic inflammation caused by HCV infection.

Approximately 1% of 3-DAA-treated subjects experienced a post-baseline ALT elevations of ≥Grade 3. These ALT elevations were generally asymptomatic and occurred during the first 28 days of study drug treatment. There were no Hy's law cases based on review by an independent hepatic expert panel. Most subjects experienced improvement or resolution by the Final Treatment Visit or by PTW4, and, in most cases, the ALT elevation resolved with continued DAA treatment; and, concomitant systemic estrogen-containing medication use was identified as a specific risk factor for ALT elevation.

- **Phase 2 Liver Function Abnormalities**

In Study M11-652, 6/571 (1%) subjects had a ≥Grade 3 ALT elevation during treatment. All six subjects completed their assigned study drug treatment. The frequency of ALT elevations was higher in subjects who received ABT-450/r 200/100 mg (5%) compared to those who received a 150 or 100 mg dose (<1%). One subject with a Grade 2 ALT elevation discontinued treatment due to cholestatic hepatitis.

The five subjects with ALT elevations ≥Grade 3 in Study M11-652 are described in the following table. One of the cases (#5025) was reviewed by the Expert Hepatic Panel. Of note, these subjects received the 200 mg dose of ABT-450.

**Table 24 Cases of transaminitis in Study M11-652**

| Subject | Case review | Reviewer comments |
|---|---|---|
| 5025 | 59 yo male treated with ABT-450/r 150/100 + ABT-267 + ABT-333 + RBV x 12 weeks. Baseline ALT 107 U/L and bilirubin 0.52 mg/dl. ALT decreased to 63 U/L at Day 8, and began to increase on Day 15. On Day 22, ALT peaked at 298 U/L, with an associated AST increase to 119 U/L. A concurrent adverse event of increased ALT was reported. Study drugs were continued without interruption or modification. Serum ALT level peaked on Day 22, and then declined with ongoing study drug administration. ALT was WNL by Day 71. Total Bilirubin was elevated on Day 8 (2.7 mg/dl) and Day 25 (1.3 mg/dl), otherwise WNL. Alkaline phosphatase was WNL. Subject achieved SVR. | This case was reviewed by the Applicant's Expert Hepatic Panel. See Table 29 |
| 5295 | 62 yo male treated with ABT-450/r 200/100 mg + ABT-267 + RBV x 12 weeks. Baseline ALT 62 U/L. Day 10 ALT 51 U/L. Day 17 ALT 229 U/L, AST 100 U/L. Study drugs were continued without interruption or modification. Day 20 ALT 186 U/L and continued to gradually decline to 53 U/L by day 45. ALT then fluctuated between 37 U/L and 53 U/L through the end of study drug treatment. ALT was 16 U/L by day 101 (Post-Treatment day 17). Total bilirubin and alkaline phosphatase remained WNL throughout study drug administration. Subject achieved SVR. | Probably related to study drugs as the pattern of on-treatment ALT increases without other etiologies identified, was consistent with other cases. |
| 5471 | 43 yo female treated with ABT-450/r 200/100 mg + ABT-267 + RBV x 12 weeks. Baseline ALT 47 U/L. Day 15, ALT 222 U/L, with AST 111 U/L. Study drugs were continued without interruption or modification, and desloratadine was discontinued on day 45. Between day 15 and the end of treatment serum ALT fluctuated between 174 U/L and 69 U/L. ALT was 17 U/L on Day 98 (Post-Treatment day 15). Alkaline phosphatase 107 U/L on day 57 (107 U/L) and 120 U/L on Day 70. Total bilirubin remained WNL during study drug | Probably related to study drugs as the pattern of on-treatment ALT increases without other etiologies identified, was consistent with other cases. |

| | | |
|---|---|---|
| | administration. Subject achieved SVR. | |
| 5717 | 35 yo female treated with ABT-450/r 200/100 mg + ABT-267 + RBV x 12 weeks. Subject was taking the estrogen-containing contraceptive Anovlar. Baseline ALT 27 U/L. ALT began to increase by Day 8 and peaked at 203 U/L on day 29, with AST that peaked at 67 U/L on Day 22. Study drugs were continued without interruption or modification. After day 29, serum ALT fluctuated between 76 U/L and 170 U/L. ALT was 13 U/L by Day 100 (Post-Treatment day 15). Total bilirubin fluctuated between 29 U/L – 62 U/L, most of which was indirect bilirubin. Alkaline phosphatase remained WNL throughout study drug administration. Subject achieved SVR. | Possibly related to co-administration of estrogen-containing medication and study drugs. |
| 8074 | 58 yo male treated with ABT-450/r 200/100 mg + ABT-267 + RBV x 12 weeks. Baseline ALT 85 U/L. ALT increased until it peaked at 408 U/L on day 15, with AST 153 U/L. Study drugs were continued without interruption or modification. ALT remained elevated through day 29, and then declined to 50 U/L by day 78. ALT was 38 U/L by Day 85. Total bilirubin and alkaline phosphatase remained WNL. Subject achieved SVR. | Probably related to study drugs as the pattern of on-treatment ALT increases without other etiologies identified, was consistent with other cases. |

No subjects in Study M14-103 had an ALT elevation above Grade 1, and there were no hepatic-related clinical events in that trial.

One subject in Study M12-999 had elevation of ALT levels to at least 3 × ULN and of total bilirubin to at least 2 × ULN (biochemical criteria for Hy's law). This subject had a peak (day 92) bilirubin of 2.1 mg/dL, which was predominantly indirect, and a peak ALT level of 175 U/L on Day 85. Because of an ongoing grade 1 ALT elevation through the treatment period, the subject underwent a liver biopsy, which ruled out drug-induced liver injury or rejection and was otherwise consistent with resolving HCV infection. The bilirubin level returned to normal on Day 120. The ALT elevation resolved on post-treatment day 4. The subject completed study drug without interruption and achieved $SVR_{12}$.

- **Phase 3 Liver Function Abnormalities**

Tables 25, 26 and 27 show (1) the mean (SD) maximum post-baseline ALT, AST and alkaline phosphatase levels, (2) maximum post-baseline elevations in ALT, AST and alkaline phosphatase levels, and (3) potentially clinical significant LFT abnormalities observed in the Phase 3 trials. The data demonstrate that, compared to PBO, which likely reflects the natural history of HCV, treatment with DAAs ± RBV decreased ALT and AST levels, increased bilirubin levels (more so when co-administered with RBV), and had a moderate effect on increasing alkaline phosphatase levels (more so in cirrhotics).

**Table 25 Mean change in LFTs from baseline to final treatment visit**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic n=1166 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO* N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| **ALT (U/L)** | -48.02 (43.49) | -48.8 (44.17) | -3.4 (20.92) | -49.7 (332.35) | -80.7 (47.12) |
| **AST (U/L)** | -28.98 (26.53) | -28.56 (23.98) | -1.8 (20.50) | -2.4 (840.17) | -68.2 (54.77) |
| **Alk phos (U/L)** | +7.46 (15.63) | +12.13 (16.76) | -0.9 (7.725) | -1.3 (27.83) | -2.3 (22.11) |
| **Bilirubin (mg/dl)** | +0.15 (0.52) | +0.64 (0.27) | -0.05 (0.20) | +0.35 (0.80) | +0.10 (0.59) |

*During Double-Blind treatment period

**Table 26 Maximum post-baseline on-treatment CTCAE Grade 1, 2, 3, and 4 LFT elevations**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic n=1171 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO* N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| **ALT** | | | | | |
| **-Grade 1 (>3.0 x ULN)** | 190(16) | 101 (20) | 180 (70) | 93 (45) | 84 (49) |
| **-Grade 2 (>3-5 x ULN)** | 13 (1) | 8 (2) | 31 (12) | 4 (2) | 0 |
| **-Grade 3 (>5-20 x ULN)** | 9 (<1) | 1 (<1) | 3 (2) | 4 (2) | 0 |
| **-Grade 4 (>20 x ULN)** | 3 (<1) | 0 | 0 | 2 (1) | 0 |
| **AST** | | | | | |
| **-Grade 1 (>3.0 x ULN)** | 154 (13) | 78 (15) | 188 (74) | 104 (50) | 85 (50) |
| **-Grade 2 (>3-5 x ULN)** | 6 (<1) | 4 (<1) | 22 (9) | 8 (4) | 1 (<1) |
| **-Grade 3 (>5-20 x ULN)** | 6 (<1) | 1 (<1) | 4 (2) | 0 | 0 |
| **-Grade 4 (>20 x ULN)** | 0 | 0 | 0 | 1 (<1) | 0 |
| **Alkaline phosphatase** | | | | | |
| **-Grade 1 (ULN – 2.5 x)** | 86 (7) | 50 (10) | 15 (6) | 44 (21) | 35 (20) |
| **-Grade 2 (>2.5 x – 5 x)** | 0 | 0 | 0 | 1 (<1) | 0 |
| **-Grade 3 (>5 x – 20 x)** | 0 | 0 | 0 | 0 | 0 |
| **-Grade 4 (>20 x ULN)** | 0 | 0 | 0 | 0 | 0 |
| **Bilirubin** | | | | | |
| **Grade 1 (>ULN-1.5 x)** | 274 (23) | 45 (9) | 8 (3) | 58 (28) | 53 (31) |
| **Grade 2 (>1.5-3.0 x)** | 215 (18) | 29 (6) | 2 (<1) | 58 (28) | 65 (38) |
| **Grade 3 (>3.0-10 x)** | 42 (3.5) | 2 (<1) | 0 | 28 (13.5) | 9 (5) |
| **Grade 4 (>10 x ULN)** | 1 (<1) | 1 (<1) | 0 | 0 | 0 |

*During Double-Blind treatment period

**Table 27 Subjects meeting criteria for potentially clinically significant LFT values**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic n=1171 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO* N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| **ALT >5 x ULN and ≥2 x baseline** | 10 (1) | 1 (<1) | 0 | 6 (3) | 0 |
| **AST >5 x ULN and ≥2 x baseline** | 6 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| **Alk phos >1.5 x ULN** | 2 (<1) | 1 (<1) | 0 | 11 (5) | 6 (3.5) |
| **Bilirubin ≥2 x ULN** | 136 (12) | 9 (2) | 0 | 58 (28) | 37 (21.5) |

*During Double-Blind treatment period

**Table 28 Combined ALT and bilirubin elevations**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic N=1171 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO[1] N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| **ALT ≥3x ULN and Bilirubin ≥2 x ULN[2]** | 8 (<1) | 0 | 0 | 8 (4) | 0 |
| **ALT ≥3x ULN and Bilirubin <2 x ULN** | 19 (2) | 9 (2) | 43 (17) | 2 (1) | 0 |
| **ALT ≥5x ULN and Bilirubin <2 x ULN** | 8 (<1) | 1 (<1) | 10 (4) | 1 (<1) | 0 |
| **ALT <3x ULN and Bilirubin ≥2 x ULN** | 130 (11) | 10 (2) | 0 | 50 (24) | 36 (22) |

1. During Double-Blind Treatment period
2. Hy's law Quadrant of eDish

The Applicant convened an Expert Hepatic Review Panel consisting of two hepatologists and another expert in drug-induced liver injury to review cases that met the biochemical criteria for Hy's law (ALT or AST >3 x ULN with total bilirubin >2 x ULN).

Of note, increases in alkaline phosphatase were typically in the Grade 1 range, were asymptomatic, not associated with adverse events or elevations of other liver enzymes, resolved with continued DAA dosing, and none of the 16 subjects with ALT ≥3x ULN and bilirubin ≥2 x ULN had an alkaline phosphatase >2 x ULN (see Tables 26 and 27).

The panel evaluated 32 subjects: 19 with ALT levels ≥3 x ULN and total bilirubin ≥2 x ULN, and 13 with ALT levels ≥5 x ULN and total bilirubin <2 x ULN:

- Thirty-one subjects received 3-DAA + RBV and one 3-DAA alone
- One subject was in the Phase 2 Study M11-652 and the others were in Phase 3 trials
- All subjects treated with ABT-450/r 150/100 mg
- The mean time to ALT elevation was 20 days (range 8-57)
- 18 subjects were male and 14 were female
- Eight subjects had cirrhosis
- Seven were females taking an estrogen-containing product (see below)
- Twenty-six subjects had no change in their DAA treatment
    - Three subjects discontinued study drugs: metformin associated lactic acidosis/death, possible drug toxicity, and acute hepatitis with estrogen use
    - Three subjects interrupted study drugs for one to seven days: two due to transaminitis with estrogen use, one for transaminitis, and one for possible steroid toxicity
- Twenty-eight subjects (87.5%) achieved SVR

The Panel assessed all cases as hepatocellular drug-induced liver injury with adaptation, but no clinical cases of Hy's law were identified. The Panel concluded that in many cases the elevations in total bilirubin were predominantly indirect and temporally inconsistent with Hy's law in that they preceded the peak serum ALT elevations, a result more likely consistent with inhibition of bilirubin transporters by ABT-450 or exacerbation by RBV-induced hemolysis.

The Panel conducted a separate review of 10 subjects randomized to placebo that met the above criteria and determined that three had possible drug-induced liver injury, four were unlikely to be drug-induced liver injury, and three were unrelated to treatment.

The Panel did not review cases for subjects with ALT 3-5 x ULN and total bilirubin <2 x ULN because they were not considered clinically relevant.

**Table 29 Hepatotoxicity cases evaluated by expert hepatic panel**

| Subject Study # | Case review | Expert Panel Assessment and comments | Reviewer Comments |
|---|---|---|---|
| **ALT ≥3 × ULN and total bilirubin ≥2 x ULN** | | | |
| 5025 M11-652 | See Table 29 above for case description. | Not a potential Hy's law case/ probably related Mild severity, transient with | Agree with assessment |

| | | | |
|---|---|---|---|
| | | ongoing drug; adaptation; total bilirubin met 2 x ULN criteria, but occurred prior to serum ALT elevation | |
| 100205 M11-646 | 52 yo female treated with OL 3-DAA (ABT-450/r 150/100) + RBV. The ALT level prior to starting active study drugs was 54 U/L. On day 93 (OL day 6), ALT 38 U/L and total bilirubin peaked at 2.9 mg/dl. On day 99 (OL day 12), ALT increased to 573 U/L and total bilirubin improved to 0.9 mg/dl. On day 101 (OL day 14), ALT further increased to 753 U/L and the concomitant medication of estrogen NOS with testosterone was discontinued. The subject reported no corresponding symptoms and admitted to having 64 oz margarita and 3 shots of tequila within 1 week prior to the elevation. The ALT further increased to a peak level of 893 U/L on day 103 (OL day 16) and study drugs were interrupted. On day 107 (OL day 20), 4 days after the last dose of study drug, ALT improved to 385 U/L and continued to improve through day 110 (OL day 23). Study drugs were reintroduced on day 113 (OL day 26). On day 117 (OL day 30), ALT was 131 U/L and total bilirubin was 2.0 mg/dl. On day 127 (OL day 40), ALT increased to 321 U/L, total bilirubin improved to 0.6 mg/dl. From there, both ALT and total bilirubin levels fluctuated, but showed gradual improvement and normalized by the end of study drug treatment. Alkaline phosphatase and INR remained WNL. Subject achieved SVR. | Not a potential Hy's law case/ Probable DILI related to study drug Upon study drug restart may have had positive rechallenge, followed by decline to normal with continued study drug. Peak bilirubin not temporally associated with peak ALT, and predominantly indirect, therefore not a potential Hy's law case. Subject receiving estrogen-containing therapy | Probably related to interaction between DAAs and estrogen-containing product |
| 111109 M13-099 | 25 yo cirrhotic female treated with 3-DAA + RBV x 12 weeks. Baseline ALT 74 U/L and total bilirubin 1.2 mg/dl. On day 8, the subject experienced a SAE of acute hepatitis with an ALT elevation of 233 U/L and total bilirubin elevation to 3.7 mg/dl. On day 10, ALT 497 U/L and total bilirubin 4.3 mg/dl. On day 10, study drugs were permanently discontinued. Concomitant medications included Eugynon (progestogen levonorgestrel and ethinyl estradiol), ibuprofen, and cetirizine. The subject experienced a pruritic rash from day 4 to 11 (Post-Treatment day 1). The adverse event of dysuria started on day 9 and nausea started on day 10. On day 12 (Post-Treatment day 2), ALT reached a peak level of 819 U/L and total bilirubin had improved to 1.9 mg/dl. The ALT and total bilirubin continued to improve from day 13 (Post-Treatment day 3). Total bilirubin was WNL by day 29 (Post-Treatment day 19) and ALT was improved to 144 U/L. ALT further improved towards baseline on day 71 (Post-Treatment day 61) with ALT 63 U/L. Alkaline phosphatase and INR remained WNL. The subject refused a follow-up liver biopsy, but continued in the study for Post-Treatment follow-up. | Not a potential Hy's law case because peak total bilirubin levels declined at time of peak ALT<br><br>Highly likely DILI<br><br>Subject receiving Eugynon. Discontinued study drugs and ALT levels declined. | Probably related to interaction between DAAs and estrogen-containing product |
| 112104 M13-099 | 64 yo cirrhotic female treated with 3-DAA (ABT-450/r 150/100) + RBV x 12 weeks. Baseline ALT 114 U/L and bilirubin 0.5 mg/dl. Day 8 ALT 39 U/L, AST 84 U/L, bilirubin 4.9 mg/dl (indirect 2.9 mg/dl). Subject experienced decreased hemoglobin (9.6 mg/dL) and RBV reduced on day 20, again on day 31, and again on day 76. On day 71 ALT 147 U/L, AST 142 U/L, bilirubin 2.7 mg/dl. | Not a potential Hy's law case/ Probable DILI Delayed ALT elevation, but consistent with mild DILI in a cirrhotic | Grade 2 ALT elevation and hemolytic anemia<br><br>Subject was taking systemic estradiol, so cannot rule out |

| | | | |
|---|---|---|---|
| | On day 85 ALT 75 U/L and bilirubin 2.8 mg/dl. On final study day, ALT 16 U/L, AST 25, bilirubin 0.4 mg/dl (day 251). Subject taking concomitant estradiol po. Alkaline phosphatase and INR WNL, and there was no change in study drugs. Subject achieved SVR. | subject. AST greater than ALT at Week 6 consistent with lab parameters in a cirrhotic. Composition of total bilirubin mixed with some indirect and direct bilirubin. Bilirubin transporter manifestation may be modified in cirrhotics. Hypothesis could be impaired elimination of conjugated bilirubin in the setting of cirrhosis and RBV induced hemolysis could bring out this impairment, accounting for the rise in conjugated bilirubin. | an interaction between DAAs and estrogen-containing product |
| 114504<br>M13-961 | 49 yo male treated with 3-DAA + RBV. Baseline ALT 162 U/L and bilirubin 0.5 mg/dl. On day 8, ALT decreased to 135 U/L but remained at Grade 2. A gradual decline in ALT occurred over the next two weeks with an ALT of 105 U/L on day 22. ALT increased to 181 U/L (Grade 2) on day 29. ALT gradually declined through the end of study drug treatment, was 97 U/L at the last visit (day 85), and further declined to 70 U/L on Day 113 (Post-Treatment day 28). Subject also experienced asymptomatic total bilirubin levels >2 x ULN on day 8 (2.9 mg/dl) and day 85 (2.6 mg/dl). Total bilirubin levels remained above ULN, but below 2 x ULN, for the duration of treatment; however, direct bilirubin levels remained only slightly elevated or normal with the highest values of 0.6 mg/dl on days 8 and 85. Alkaline phosphatase and INR remained normal. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Not a Hy's Law case/unlikely DILI The pattern of ALT elevation is more consistent with natural history of hepatitis C | It is not clear how this is natural history of HCV as the ALT initially declined along with decrease in HCV RNA |
| 132101<br>M13-099 | 63 yo male treated with 3-DAA + RBV (ABT-450/r 150/100) x 12 weeks. Baseline ALT 165 U/L and bilirubin 2.3 mg/dl. On day 8 ALT improved to 68 U/L and total bilirubin level increased to 2.9 mg/dl with an indirect bilirubin of 2.3 mg/dl. On day 15, ALT increased to 170 U/L and total bilirubin reached a maximum at 3.6 mg/dl. On day 29, ALT reached a maximum level at 179, while total bilirubin returned towards baseline 2.1 mg/dl. By day 57, and for the remainder of the treatment period, ALT levels were WNL and total bilirubin levels were better than baseline level. Alkaline phosphatase and INR remained WNL throughout. Study drugs were not interrupted or discontinued. Subject achieved SVR | Not a potential Hy's law case/ Possible DILI Minor elevation in serum ALT which normalized prior to end of treatment | Grade 2 asymptomatic ALT elevation<br><br>Agree mild DILI |
| 142101<br>M13-099 | 67 yo male treated with 3-DAA + RBV x 12 weeks. Baseline ALT 145 U/L and bilirubin 0.7 mg/dl. On day 8, ALT increased to 250 U/L. Dehydration and weakness concurrent adverse events which began on day 6, while | Not a potential Hy's law case/ Possible DILI. May be cirrhosis | It is not clear how this case could be attributed to RBV-induced hemolysis |

| | | | |
|---|---|---|---|
| | increased hepatic enzymes was considered an AE on day 8. The subject developed bronchitis on day 10 and was treated with prednisone, salbutamol inhaler, and benzonatate. Day 29 bilirubin increased to 2.5 mg/dl. The subject had started oxycocet (10/300 mg as needed) on day 27 for shoulder and back pain. On day 35, ALT and total bilirubin levels further increased to 328 U/L and 3.7 mg/dl, respectively, with the bilirubin elevation being predominantly indirect. The oxycocet was discontinued on day 43 due to the ALT elevation. On day 58, ALT improved to 49 U/L and total bilirubin decreased to 1.6 mg/dl. ALT improved to 21 U/L by end of treatment on day 85. Study drugs were not interrupted or discontinued. On day 113 (Post-Treatment day 28), ALT was 42 U/L and total bilirubin was 0.4 mg/dl. Alkaline phosphatase and INR remained WNL. Subject achieved SVR. | modifying transporter drug effect in the setting of increased hemolysis due to RBV | as there is no mention of this subject having hemolytic anemia or a dose modification of RBV |
| 202203 M11-646 | 19 yo female treated with 3-DAA + RBV. Baseline ALT was 24 U/L. On day 8, ALT increased to 190 U/L and total bilirubin was elevated to 1.9 mg/dl, predominately indirect bilirubin. Adverse event of somnolence was reported from day 2 to day 20, headache and dizziness since day 3, fatigue since day 5, nausea on day 6, vomiting (2 episodes) from day 7 to day 20, and increased ALT on day 8. Concurrent medications included quetiapine, which was dose reduced from 12.5 to 6.25 mg daily on day 5 and discontinued on day 11. ALT rapidly increased to 556 U/L on day 12 and Marvelon (ethinylestradiol/desogestrel) was discontinued. ALT further increased to a maximum of 876 U/L on day 15. On day 26, melatonin was started for insomnia. By day 29, ALT improved to 167 U/L. Mometasone was started for bilateral pedal skin peeling on day 35. On day 41, miconazole, betamethasone, and clotrimazole were started for a vaginal yeast infection. ALT fluctuated between 257 and 450 U/L through day 78. Total bilirubin fluctuated between 0.9 and 1.6 mg/dl through day 64. The subject started another course of miconazole from day 68 to 70. On day 71, total bilirubin increased to 2.2 mg/dl with an elevated alkaline phosphatase at 123 U/L. Total bilirubin improved to 1.1 mg/dl on day 78. On day 84, ALT was elevated at 293 U/L and total bilirubin peaked at 2.9 mg/dl. INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Not a potential Hy's law case/ Probable DILI related to study drugs<br>The initial hepatocellular injury was probably due to study drug. The later elevation in bilirubin is predominantly indirect, suggesting that this is secondary to the bilirubin transporter inhibition known for ABT-450 and unrelated to earlier liver injury | Probably related to interaction between DAAs and estrogen-containing product |
| 203107 M13-099 | 60 yo male with cirrhosis treated with 3-DAA + RBV x 12 weeks. Baseline ALT 92 U/L and bilirubin 0.8 mg/dl. On day 15, the ALT increased to 258 U/L. Bilirubin was 2.0 mg/dl on day 8 improved to 1.4 mg/dl at the time of the Grade 3 ALT elevation on day 15. Concurrent adverse events of muscle cramps localized to the right leg and elevated ALT were reported at that time. The only concomitant medication was metformin. The ALT peaked at 265 U/L on day 22. The ALT improved to 93 U/L by day 71. The total bilirubin level fluctuated between 1.0 and 1.7 mg/dl through day 71 and was predominantly indirect. On day 85, the ALT level was 155 U/L, total bilirubin was 2.5 mg/dl. Study drugs were not interrupted or discontinued. On day 112 (Post –Treatment day 27), ALT 46 U/L and total bilirubin 0.4 mg/dl. Alkaline phosphatase and INR remained WNL. Subject achieved SVR. | Not a potential Hy's law case/ Probable DILI<br>Doubling in ALT, with a second elevation separated by about 2 months. Double elevations are observed in DILI, but separation by 2 months is unusual. Resolution in the Post-Treatment Period. | Agree with assessment |
| 213502 | 55 yo female treated with 3-DAA + RBV. Baseline ALT 69 | Not a potential | Agree with |

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| M13-961 | U/L. Day 8 ALT 82 U/L and bilirubin 3.7 mg/dl with jaundice. Day 15 ALT 234 U/L, bilirubin 1.75 mg/dl. Study drugs were continued without interruption or modification. ALT level began to decline on Day 20 and was 26 U/L by Day 70. Alkaline phosphatase remained WNL throughout. Subject achieved SVR. | Hy's law case<br>Probable DILI<br>The total bilirubin elevation preceded the ALT rise and was predominantly unconjugated, so not consistent with Hy's law. Mild injury with adaptation | assessment |
| 382123<br>M13-099 | 64 yo cirrhotic female treated with 3-DAA + RBV x 12 weeks. See discussion under Deaths for additional information. | SAE/Death<br>Not a potential Hy's law case/<br>Not related<br>Clear alternative etiology of metformin-induced lactic acidosis and shock liver | Agree with assessment |
| 400305<br>M13-098 | 57 yo female treated with OL 3-DAA + RBV. Baseline ALT 23 U/L and bilirubin 0.6 mg/dl. Day 110 (OL day 25): acute biliary colic with duct stones, ALT 260 U/L. AST 309 U/L and bilirubin 15 mg/dl. Subject underwent ERCP on day 29 and then a post treatment cholecystectomy. ALT, AST and bilirubin normalized. ALT and AST returned to WNL by day 127 (OL day 42), with total bilirubin reaching normal limits by day 141 (OL day 56). INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Reported as SAE<br>Not a potential Hy's law case/<br>Not related to study drug<br><br>Alternative etiology common bile duct stone | ABT-450 caused gall bladder erosions in preclinical studies. This case was one of four gall-bladder related SAEs. A relationship with ABT-450 cannot be ruled out |
| 403307<br>M13-098 | 60 yo male treated with OL 3-DAA + RBV. Day 1 of OL treatment, ALT 30 U/L and bilirubin 0.9 mg/dl. On day 92 (OL day 7), ALT decreased to 19 U/L, and total bilirubin increased to 4.4 mg/dl and an adverse event of increased blood bilirubin was reported. Total bilirubin increase was predominantly indirect. On days 95 (OL day 10) and 98 (OL day 13), the subject experienced nephrolithiasis and ureteral calculi. On day 101 (OL day 16), ALT increased to 440 U/L. A concurrent adverse event of increased transaminases was reported. From day 108 to day 140 (OL day 23 to day 55), ALT fluctuated between 179 and 382 U/L and total bilirubin fluctuated between 1.0 and 1.6mg/dl. The event of increased blood bilirubin was considered resolved on day 108 (OL day 23) with total bilirubin level at 1.2 mg/dl. On day 147 (OL day 62), an ureteroscopy with stone extraction was performed. ALT further declined to 137 U/L by day 155 (OL day 70), and reached normal limits by the end of treatment on day 169 (OL day 84). Alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Not a potential Hy's law case/<br>Highly likely DILI with adaptation and related to study drug<br>Indirect hyperbilirubinemia likely due to active drug | Agree with assessment |
| 404303<br>M13-098 | 38 yo female treated with 3-DAA + RBV. Baseline ALT 25 U/L and bilirubin 0.8 mg/dl. Day 15 ALT increased to 126 U/L. Concomitant medications included NuvaRing®, ibuprofen, and etoricoxib. Serum ALT declined to normal (28 U/L) by day 29; NuvaRing was discontinued the same day. AST increased to 55 U/L on day 15 and was WNL by day 29. Total bilirubin, which was predominantly indirect bilirubin, fluctuated between 1.8 and 3.5 mg/dl from day 8 to day 85 and improved to 1.3 mg/dl on day 113 (Post- | Not a potential Hy's law case/<br>Possible DILI with adaptation related to study drug; however, ALT increase small and transient. Rise in indirect bilirubin | Probably related to interaction between DAAs and estrogen-containing product |

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| | Treatment day 28). Alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | drug effect – not DILI | |
| 405207<br>M11-646 | 21 yo male treated with OL 3-DAA + RBV. Baseline ALT 58 U/L and bilirubin 0.7 mg/dl. On day 15, ALT increased to 288 U/L. Adverse event of ALT increased was reported on day 8. ALT fluctuated between 343 U/L and 197 U/L from day 22 to day 85. ALT was WNL by day 113 (Post-Treatment day 28). Total bilirubin, which was predominantly indirect bilirubin, fluctuated between 1.2 and 3.0 mg/dl from day 8 to day 79 and was WNL by day 85. Alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Not a potential Hy's law case/ Possible DILI related to study drug with adaptation as no other cause evident. Bilirubin elevation unconjugated and consistent with a direct drug effect | Agree with assessment |
| 440305<br>M13-098 | 54 yo male treated with 3-DAA + RBV. Baseline ALT 139 U/L and bilirubin 0.8 mg/dl. On day 15, ALT increased to 288 U/L. Concomitant medications included paracetamol, glucosamine, fish oil, and manuka honey. ALT fluctuated between 343 U/L and 197 U/L from day 22 to day 85. ALT was WNL by day 113 (Post-Treatment day 28). Total bilirubin, which was predominantly indirect bilirubin, fluctuated between 1.2 and 3.0 mg/dl from day 8 to day 79 and was WNL by day 85. Alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR. | Not a potential Hy's law case/ Unlikely DILI Likely represents waxing and waning of background chronic HCV infection | It is not clear how this is natural history of HCV as the ALT initially declined along with decrease in HCV RNA |
| 606111<br>M13-099 | 57 yo cirrhotic male treated with 3-DAA + RBV x 12 weeks. Baseline ALT 147 U/L, bilirubin 1.5 mg/dl, and alkaline phosphatase was 174 U/L. On day 2, the subject experienced abdominal pain and on day 5 experienced "liver ache." On day 17, the subject developed a "painful pancreas" and had pale stools. On day 25, the subject developed mild ascites and a sore mouth and tongue. On day 44, the subject was noted to have a weight increase of 8.7 kg since starting the study and spironolactone was started. Other concomitant medications included paracetamol (1,000 mg daily for abdominal pain since day 2), dihydrocodeine, fluticasone, hydroxyzine, montelukast, salbutamol inhaler, and omeprazole. On day 51, ALT reached a peak level of 509 U/L, and total bilirubin was 2.5 mg/dl. The adverse event of increased ALT started on day 51. On day 54, the ALT improved to 286 U/L and total bilirubin peaked at 3.5 mg/dL, which was predominantly indirect bilirubin. A urine drug screen detected opiates, confirmed as hydrocodone and dihydrocodone, On day 54, the subject had a weight decrease (12.4 kg) and montelukast and spironolactone were discontinued. On day 57, study drugs were interrupted due to a serious adverse event of steroid toxicity and fluticasone was discontinued. On day 61, dihydrocodeine dosing was modified and salbutamol was discontinued. On day 64, the ALT level further improved to 114 U/L, and study drugs were restarted. By day 85, ALT level improved to 50 U/L and total bilirubin was 2.9 mg/dL. Childs-Pugh classification changed to class B due to elevated bilirubin and the presence of slight ascites. On day 113 (Post-Treatment day 28), the ALT level was 57 U/L and total bilirubin was 0.7 mg/dL. Alkaline phosphatase fluctuated between 136 and 327 U/L during study drug treatment. INR remained WNL. The subject's Post-Treatment Week | Not a potential Hy's law case/ Possible DILI Small elevation in ALT could be natural history of underlying disease. Possible underlying fatty liver disease | It is not clear how this is natural history?<br><br>Do not agree that ALT elevations to >5x ULN are “minor” especially with bilirubin elevation at almost 2x ULN.<br>Seems more likely to be study drug related toxicity.<br><br>Subject did successfully complet study but still had ongoing inflammation post-treatment. |

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| | 12 ALT level again increased to 130 U/L and total bilirubin increased to 3.0 mg/dL. Upon retest several weeks later, the ALT level improved to 101 U/L and total bilirubin was at 2.3 mg/dL. Subject achieved SVR | | |
| 760206 M11-646 | 63 yo male treated with 3-DAA + RBV. Baseline ALT 99 U/L and bilirubin 1.0 mg/dL. On day 8, total bilirubin reached 2.6 mg/dL, predominantly indirect (2.2 mg/dL), ALT 60 U/L. On day 14, ALT increased to 134 U/L, while total bilirubin decreased to 2.1 mg/dL. Thereafter, both ALT and total bilirubin levels continued to gradually decline with total bilirubin consistently comprised of predominantly indirect bilirubin. On day 55, the total bilirubin was 1.0 mg/dL and on day 71 ALT was 36 U/L. On day 85 (Post-Treatment day 1), ALT was 49 U/L and total bilirubin was 1.7 mg/dL. ALT and total bilirubin were within their respective normal reference ranges on day 113 (Post-Treatment day 29). Alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Not a potential Hy's law case/ Not related to study drug<br>Very low elevation in serum ALT, not considered an "event;" trivial increase. Early bilirubin rise is largely indirect and did not represent DILI | Agree with assessment |
| 782303 M13-098 | 58 yo male treated with 3-DAA + RBV. Baseline ALT 73 U/L and bilirubin 17 mcmol/L. On day 14, ALT increased to 297 U/L. On day 21, ALT peaked at 437 U/L and declined to 422 U/L on day 27. Adverse event of increased transaminases was reported on day 21. Subject also complained of nausea days 3-16, jaundice days 6-18 and asthenia day 7. Urine drug screen results on day 27 showed Barbiturates and Opiates "Detected (unconfirmed)." On day 23, study drugs were discontinued. The subject withdrew consent and was discontinued from the study. Baseline total bilirubin was 1.0 mg/dL on day 1, increased to 5.0 mg/dL on day 8, which was predominantly indirect bilirubin, and gradually declined to 1.0 mg/dL on day 27 (Post-Treatment day 4). Alkaline phosphatase and INR remained WNL. Subject did not achieve SVR | Not a potential Hy's law case/ Probable DILI related to study drug<br><br>Elevation in bilirubin preceded ALT elevation and mostly unconjugated, not a potential Hy's law case. Elevation in ALT may represent DILI | Agree with assessment |
| **ALT ≥5 × ULN and total bilirubin <2 × ULN** | | | |
| 100202 M11-646 | 33 yo male treated with 3-DAA + RBV. Baseline ALT 129 U/L. Day 29 ALT 228 U/L, day 44 ALT160 U/L, day 88 ALT 102 U/L, day 113 ALT 106 U/L. Bilirubin, alkaline phosphatase and INR WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Unlikely related. Trivial increase and may be consistent with natural history, but cannot rule out a low level effect of DAAs | Agree with assessment |
| 100214 M11-646 | 57 yo male treated with 3-DAA + RBV. Baseline ALT was 180 U/L. On day 9, ALT increased to 430 U/L and was 833 U/L on day 15. ALT rapidly declined to 513 U/L by day 20. Study drug was interrupted on day 20 and was restarted on day 21. ALT further declined to 77 U/L by day 43 and was WNL on day 57. ALT then fluctuated between 65 and 99 U/L from day 70 to 85. Total bilirubin peaked at 22 mcmol/L on day 9 and then remained WNL; alkaline phosphatase and INR remained WNL. Subject achieved SVR | Probably DILI (acute necroinflammatory response) with adaptation. Missed dose does not really factor into analysis. The elevation was short-lived without consequence | Agree with assessment |
| 117407 M14-002 | 56 yo male treated with 3-DAA. Baseline ALT 110 U/L and bilirubin 0.4 mg/dL. Day 16 ALT 268 U/L. Taking cold medications with Tylenol and alcohol for URI days 9-15. Day 19 ALT 278 U/L, day 22 ALT declining, day 85 ALT 43 U/L. Bilirubin, alkaline phosphatase WNL throughout. | Probable DILI and related to study drugs<br>Timing of ALT increase consistent | Agree with assessment |

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| | Subject achieved SVR | with other cases, but without liver fibrosis present | |
| 125406 M14-002 | 68 yo female treated with 3-DAA + RBV. Baseline ALT 365 U/L and bilirubin 0.g mg/dL. On day 8, ALT improved to 136 U/L, AST improved to 53 U/L, and total bilirubin increased to 2.2 mg/dL, which was predominantly indirect (1.7 mg/dL). A concurrent adverse event of increased blood bilirubin was reported. On day 42, ALT increased to 341 U/L, AST increased to 137 U/L, and total bilirubin had improved to normal limits. A concurrent adverse event of increased ALT was reported. The subject had an abdominal ultrasound which showed lesions on the liver. MRI showed the lesions were entirely benign and not clinically significant. On day 48, ALT decreased to 254 U/L, AST decreased to 80 U/L, and total bilirubin increased to 1.4 mg/dL. Thereafter, ALT, AST and total bilirubin steadily improved reaching normal limits by day 113 (Post-Treatment day 29). Alkaline phosphatase was slightly elevated on day 42 (126 U/L), day 48 (133 U/L) and day 71 (124 (U/L), but otherwise WNL. INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Probably related to study drug Late ALT elevation with fluctuation in ALT levels not consistent with drug related ALT pattern previously observed, but no alternate cause evident | Agree with assessment |
| 126213 M11-646 | 62 yo male treated with OL 3-DAA + RBV. On day 91 (OL day 1), the subject began treatment with the active study drug regimen. The subject's latest ALT level prior to starting active study drugs was 23 U/L. On day 147 (OL day 57), ALT level increased to 298 U/L. On day 149 (OL day 59), the ALT level improved to 221 U/L. The ALT continued to improve and was 73 U/L by the end of study drug treatment, which had continued without interruption. ALT was WNL by day 203 (Post-Treatment day 28). Total bilirubin, alkaline phosphatase and INR remained WNL. Subject achieved SVR | Highly likely DILI related to study drug with adaptation Indirect hyperbilirubinemia likely due to active Drug | Agree with assessment |
| 203302 M13-098 | 36 yo female treated with 3-DAA + RBV. Baseline ALT 31 U/L. Day 15 ALT 1157 U/L. ALT 776 to 1022 U/L days 18-43. Day 38 Eugynon (ethinylestradiol/levonorgestrel) interrupted. Day 43 DAAs interrupted. Day 50 ALT 101 U/L. Day 53 DAAs restarted. Day 85 ALT 16 U/L. Alkaline phosphatase, INR and bilirubin WNL. Subject achieved SVR | Highly likely DILI related to study drug. There does not seem to be another etiology for the elevations in serum ALT other than study drug. The liver injury occurred at a time when the virus would have been cleared by active treatment. Study drug interruption occurred with a delayed positive dechallenge; however, there was a negative rechallenge, which may represent adaptation | Probably related to interaction between DAAs and estrogen-containing product |
| 214503 M13-961 | 60 yo female treated with 3-DAA + RBV. Baseline ALT 128 U/L. Day 9 ALT 148 U/L with bilirubin 2.0 mg/dL. Adverse | Probable DILI ALT almost | Agree with assessment |

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| | event of hyperbilirubinemia was reported on Day 9. The ALT level peaked on Day 15 at 297 U/L, with AST of 151 U/L and total bilirubin of 2.4 mg/dL (indirect bilirubin 1.6 mg/dL). Concurrent adverse events of increased transaminase and anemia were reported on Day 15. DAA treatment was continued without interruption or modification and ribavirin was modified due to anemia. ALT levels began to decline on Day 18 and was 27 U/L on Day 86 (Post-Treatment Day 2. Alkaline phosphatase remained WNL. Subject achieved SVR | doubled from Week 1 to Week 2 most consistent with DILI with adaptation | |
| 383303 M13-098 | 44 yo male treated with OL 3-DAA + RBV. During the blinded phase, ALT fluctuated between 173 U/L to 221 U/L Treatment day 1 ALT 177 U/L and bilirubin 0.8 mg/dL. day 99 (OL day 14), ALT 258 U/L. On day 113 (OL day 28), ALT improved to 140 U/L. ALT level continued to improve and was 39 U/L by day 169 (Post –Treatment day 1). Total bilirubin, alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Unlikely DILI Elevations throughout study period without an initial decline | Agree with assessment |
| 461207 M11-646 | 67 yo male treated with 3-DAA + RBV. Baseline ALT 168 U/L. ALT improved to 72 U/L on day 9. On day 16 ALT increased to 250 U/L and further increased to 373 U/L on day 29. ALT declined from 274 U/L on day 32 to 201 U/L on day 44. By day 57 ALT was 70 U/L, and was WNL from day 71 through the end of treatment. Total bilirubin, alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Probable mild DILI related to study drug with adaptation given fall in ALT at Week 1 | Agree with assessment |
| 462207 M11-646 | 46 yo female treated with OL 3-DAA + RBV. ALT prior to starting active study drugs was 46 U/L. On day 93 (OL day 8), the ALT level increased to 233 U/L. On day 100, ALT improved to 115 U/L. Fatigue was the only adverse event reported (from day 92 to day 100). ALT level continued to improve and was WNL by day 128. Total bilirubin, alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Highly likely DILI related to study drug Small ALT elevation with adaptation | Agree with assessment |
| 462308 M13-098 | 49 yo female treated with 3-DAA + RBV. Baseline ALT 61 U/L and bilirubin 0.3 mg/dL. ALT fluctuated between 125 U/L to 160 U/L from day 15 to day 46. On day 57, ALT increased to 174 U/L and peaked at 208 U/L on day 71. A concurrent adverse event of increased transaminases was reported on day 57. The subject experienced vomiting on day 77, which resolved the same day. Additionally, the subject experienced nausea on day 91, which resolved on day 106. ALT was 118 U/L on day 78 and 144 U/L on day 85. ALT was WNL by day 113 (Post-Treatment day 29). Total bilirubin, alkaline phosphatase and INR remained WNL. Study drugs were not interrupted or discontinued. Subject achieved SVR | Probable DILI related to study drug Serum ALT fluctuations with ongoing study drug; more prolonged elevation in serum ALT, but study drug treatment continued | Agree with assessment |
| 480303 M13-098 | 23 yo female treated with 3-DAA + RBV. Baseline ALT was 83 U/L. On day 15, ALT increased to 550 U/L. On day 19, ALT peaked at 1169 U/L. Concurrent adverse events included increased alanine aminotransferase increased on day 15, fatigue on day 16, and abdominal cramps on day 22. Eugynon (ethinylestradiol/levonorgestrel) was the only concomitant medication, and it was discontinued day 19. Study drugs were not interrupted or discontinued. ALT declined to 729 U/L on day 25 and 273 U/L on day 29. ALT was WNL by day 43. Total bilirubin fluctuated between 15 | Highly likely DILI related to study drug Short-lived necroinflammatory event despite continuing treatment with study drug. Bilirubin is not elevated, so | Probably related to interaction between DAAs and estrogen-containing product |

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| | mcmol/L and 25 mcmol/L from day 8 to day 19 and was WNL by day 25. Alkaline phosphatase was WNL from day 1 to day 29 and fluctuated between 107 U/L to 128 U/L from day 43 to day 85 (Post-Treatment day 1). INR remained WNL. Subject achieved SVR | liver function was not significantly impaired despite height of serum ALT observed | |
| 607105 M13-099 | 71 yo male treated with 3-DAA + RBV x 12 weeks. Baseline ALT 73 U/L and bilirubin 0.7 mg/dL. Day 8 ALT improved to 45 U/L. The subject experienced a cold on day 6 and nausea on day 8 and paracetamol (500 – 4,000 mg total daily dose, as needed) was started on day 12. On day 15, the ALT level increased to 186 U/L and total bilirubin increased to 2.0 mg/dL, which was predominantly indirect bilirubin. On day 25, the ALT level peaked at 242 U/L, while total bilirubin normalized to 1.2 mg/dL. The ALT level improved to 127 U/L on day 43. Paracetamol was stopped on day 46. ALT levels fluctuated between 83 and 209 U/L from day 57 to day 85 (Post-Treatment Day 1). Study drugs were not interrupted or discontinued. On day 99 (Post-Treatment day 15), ALT was 23 U/L. Alkaline phosphatase and INR remained WNL throughout the Treatment and Post-Treatment periods. Subject achieved SVR | Probable DILI Fluctuating ALT during treatment with positive de-challenge in the Post-Treatment Period | Agree with assessment |

The Applicant also conducted an SMQ search of "drug-related hepatic disorders – severe events only." This SMQ includes MedDRA preferred terms such as acute hepatic failure, fulminant hepatitis, acute hepatitis, and hepatitis cholestatic. In addition, this SMQ includes less specific hepatic preferred terms such as asterixis and ascites.

There were eight subjects had events that were captured in the SMQ search: two events of HCC, two events of ascites, and one event each of spider nevus, acute hepatitis, hepatic encephalopathy, and esophageal variceal hemorrhage. The two events of HCC were both diagnosed following completion of study treatment, and determined to be not related to study drugs. Also, both events of HCC, the event of acute hepatitis and the event of esophageal variceal bleeding were reported as SAEs. The events of acute hepatitis (Subject 111109) and ascites (Subject 606111) were reviewed by the Expert Hepatic Panel (see Table 29).

- **Liver Function Abnormalities and Estrogen-Containing Products**

Further analyses of events in Study M11-652 and early in Phase 3 trials suggested that female subjects receiving estrogen-containing products were experiencing a higher frequency of ≥Grade 3 ALT increases: 6% (7/113) compared to <1% of females not receiving estrogens.

At the time these events were observed, no drug-drug interaction studies with any hormonal contraceptives had been conducted. Pharmacokinetic data from subjects that developed ≥Grade 3 ALT elevations had ABT-450 exposures in the same range as most other subjects. Thus, a clear association between ALT elevations and systemic ABT-450 exposures was not identified. The Applicant hypothesized that a mechanism for the interaction between the DAAs and estrogen containing products may be inhibition of UGTs by the DAAs or induction of metabolic enzymes or transporters by the contraceptives.

Based on these findings the Applicant moved to contraindicate the use of concomitant estrogen-containing hormonal contraceptives in the ongoing Phase 3 trials and initiated a drug-drug interaction study (Study M12-205) to further investigate the potential interaction between the

DAAs and an estrogen-containing oral contraceptive (Ortho-Cyclen®). The study was paused due to ALT elevations (Grade 1-2) observed in the first 4/5 treated subjects. Preliminary pharmacokinetics showed $AUC_{24}$ and $C_{max}$ values were ~35% to 70% and 20% to 55% lower for ABT-450 and RTV, respectively, and $AUC_{12}$ and $C_{max}$ values ~55% to 60% and 45% to 60% lower for dasabuvir and its M1 metabolite, respectively. Subsequently, the Applicant added an arm to Study M12-205 to evaluate the pharmacokinetics, safety and tolerability of the DAAs with a low dose progestin (0.35 mg) only oral contraceptive. Results from this cohort demonstrated no ALT increases and no clinically relevant pharmacokinetic interactions between the DAAs and progestin. An additional arm of healthy females was enrolled and received the DAAs plus an ethinyl estradiol/norethindrone 0.035/0.4 mg combination oral contraceptive, and this arm was stopped early as 9/12 subjects experienced Grade 1-2 ALT elevations.

As discussed above, seven cases of ALT levels $\geq$3 x ULN and total bilirubin $\geq$2 x ULN reviewed by the Expert Hepatic Panel occurred in females during concomitant use of the 3-DAAs and estrogen-containing products (four for contraceptive use, one for dysmenorrhea, and two for hormone replacement therapy):

- Five subjects discontinued the estrogen-containing product
  - Two also interrupted the DAAs for 7-10 days; on restart of the DAAs there was no recurrence of the ALT elevation
  - Three had no change to the DAA dosing and their ALT levels normalized
- One discontinued the DAAs and continued the estrogen-containing product and her ALT levels normalized
- One continued both the DAAs and oral contraceptive with normalization of ALT
- 6/7 (86%) achieved SVR

***Reviewer comment: Hepatic transaminitis among women taking estrogen-containing products raises significant safety concerns and support that estrogen-containing products and ABT-450 probably should not be co-administered. RBV is a teratogen and during the period of concomitant DAA and RBV dosing, female patients must use at least 2 effective means of contraception. The mechanism of action between ABT-450 and estrogen has not been established, and it would likely be unsafe to conduct additional studies in healthy volunteers.***

- **Proposed Transaminitis WARNING**

The Expert Hepatic Panel concluded that with the exception of women on estrogen, monitoring of LFTs did not have an impact on liver safety, the percentage of patients experiencing ALT elevations was relatively low compared to other drug treatments where universal liver chemistry monitoring is recommended, and when monitoring detected ALT elevations, even relatively high elevations, the data suggested that continued drug treatment for the full 12 weeks was generally safe. They raised the concern that routine monitoring may result in the unnecessary discontinuation of treatment in the majority of patients experiencing ALT elevations.

Based on the above findings, the Applicant proposed [redacted] (b) (4)

***Reviewer comment: There are concerns about transaminitis among male and female subjects not receiving estrogen-containing products. Further, despite the Expert Hepatic Panel's opinion about not needing to routinely monitor patients for ALT elevations, it could be concerning to a clinician to find a significantly increased ALT level without any precautionary language about how to manage such patients, and without guidance, clinicians may inappropriately discontinue DAA treatment. Thus, it is reasonable to describe this risk information in the label.***

**Bilirubin Level Elevations**

ABT-450 is a known inhibitor of the bilirubin transporter OATP1B1, which leads to elevations of predominantly indirect bilirubin levels. Across the Phase 2 and 3 trials, bilirubin elevations were typically observed within 1 to 2 weeks of initiating treatment, were generally self-limited, declined toward baseline levels by the end of treatment, and were at or near baseline levels by PTW 4. The majority of bilirubin elevations were single episodes. In addition, RBV-induced hemolysis may also have contributed to hyperbilirubinemia, as the frequency of bilirubin elevations were generally higher among subjects treated with RBV compared to those who did not receive RBV.

The risk of ≥Grade 3 bilirubin elevations was 10% for cirrhotic subjects compared to 5% in those without cirrhosis. Signs of cholestasis such as jaundice and/or scleral icterus were reported in <1% of subjects. Most events were classified as mild and there were no SAEs related to bilirubin elevations. Less than 1% of subjects underwent a RBV dose reduction or interrupted DAA treatment due to bilirubin elevations; no subject discontinued DAA treatment due to bilirubin elevations.

As discussed above, the pattern of bilirubin elevations was different than the pattern of ALT elevations.

- **Phase 2**

In Studies M11-652, M14-103 and M12-999, the mean change in total bilirubin levels ranged from +0.11 mg/dL to +0.75 mg/dL, depending on population, regimen and duration of treatment. Maximum bilirubin increases were observed at Weeks 1-2, then declined toward baseline levels, and were mostly all normal by PTW2. A total of 14/643 (2%) subjects had a Grade 3 (>3.0 x ULN) elevation, and no subject had a Grade 4 elevation. Three subjects had jaundice, one subject with jaundice interrupted DAA, and one subject discontinued study drugs due to cholestatic hepatitis.

In Study M11-652, the 200 mg dose of ABT-450 was associated with a higher proportion of subjects with bilirubin elevations >2 x ULN (32.5%) compared to the 100 and 150 mg doses (~7%). Bilirubin elevations >2 x ULN were lowest in Group E (no RBV) at 1% compared to 14% in groups treated with RBV. Prior pegIFN/RBV null responders treated for 24 weeks had higher rates of total bilirubin elevations >2 x ULN compared to treatment naïve subjects; 16% versus 5%, respectively.

- **Phase 3**

The pattern of bilirubin elevations were comparable to those observed in the Phase 2 trials. There was a statistically significant increase in mean bilirubin levels from baseline in subjects treated with 3-DAA + RBV compared to those who did not receive RBV: +1.75 mg/dL and +0.6 mg/dL, respectively. There were no differences in the proportion of males and females with elevated bilirubin levels. Subjects treated with RBV had higher frequency of Grade 1, 2 and 3 bilirubin increases. In general, maximum bilirubin increases were observed at Week 1 (day 8), levels either stabilized or decreased during treatment, and were generally at baseline or below baseline levels by PTW 4. For many subjects, the elevated bilirubin value was observed at single time points.

On-treatment maximum bilirubin elevations from baseline to end of treatment in the Phase 3 trials are shown in Table 30.

**Table 30 Maximum on-treatment bilirubin elevations, Phase 3 Trials**

| | 3-DAA + RBV X 12 weeks Non-cirrhotic N=1165 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO[1] N=254 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| **G1 (>ULN-1.5 x)** | 274 (23) | 45 (9) | 8 (3) | 58 (28) | 53 (31) |
| **G2 (>1.5-3.0 x)** | 215 (18) | 29 (6) | 2 (<1) | 58 (28) | 65 (38) |
| **G3 (>3.0-10 x)** | 42 (4) | 2 (<1) | 0 | 28 (13.5) | 9 (5) |
| **G4 (>10 x ULN)** | 1 (<1) | 1 (<1) | 0 | 0 | 0 |

1 During Double-Blind treatment period

Nineteen non-cirrhotic subjects with ≥Grade 3 bilirubin elevations treated with 3-DAA + RBV also had clinical events of jaundice (10), jaundice with hyperbilirubinemia (2), hyperbilirubinemia (5), ocular icterus (1) or ocular icterus with hyperbilirubinemia (1). One subject with ocular icterus/hyperbilirubinemia had his RBV dose decreased and continued DAA treatment, and one subject with hyperbilirubinemia interrupted study drugs for a few days, had resolution, and restarted study drugs without recurrence. Most events were graded as mild, six were moderate and there was one severe event of hyperbilirubinemia. No events were considered serious and no subject discontinued DAA treatment. No subject in the DAA alone or PBO groups had clinical findings related to increased bilirubin levels.

Sixteen subjects in the Compensated Cirrhosis trial with ≥Grade 3 maximum bilirubin increases had clinical events including: jaundice (4 in the 12-week and 1 in 24-week arm), hyperbilirubinemia (7 in the 12-week and 1 in the 24-week arm), one jaundice and hyperbilirubinemia in the 12-week arm, and ocular icterus (1 in each arm). Six events were considered moderate and one event of hyperbilirubinemia in the 12-week arm was graded as severe. There were no SAEs, and only one subject interrupted DAA for a brief period with resolution and no recurrence.

In the Compensated Cirrhosis trial, the frequency of ≥Grade 3 bilirubin was higher in the 12-week arm. All subjects in the trial received the same treatment during the first 12 weeks. A similar proportion of subjects in both arms had maximum bilirubin elevations of at least Grade 2 (42% versus 43%), and the timing and resolution of the bilirubin elevations were the same. The

difference in Grade 3 elevations was not explained by differences in demographic or disease characteristics or RBV exposures.

***Reviewer comment: Increases in bilirubin levels appear consistent with the inhibitory effect of ABT-450 on the bilirubin transporter OATP1B1. The maximum increase from baseline in bilirubin levels was higher in subjects treated with RBV. The difference between Grade 3 bilirubin elevations in the 12 and 24 week arms in cirrhotic subjects was likely attributable to chance as no other explanation has been identified. Most clinical events were self-limited and resolved without intervention. Having cirrhosis did not significantly increase the risk of bilirubin elevations compared to not having cirrhosis. Based on these analyses, the Laboratory Abnormality section of the label should carry information about the frequency of bilirubin increases, but the data do not warrant inclusion in Warnings and Precautions.***

**Anemia**

Ribavirin (1-beta-D-ribofuranosy l-IH-1, 2, 4-triazole-3-carboxamide) is a synthetic guanosine analog. The most important treatment-limiting effect of RBV is hemolytic anemia, which appears to be due to accumulation of RBV triphosphate within the erythrocyte, which is believed to lead to oxidative damage to the red cell membrane and increased extravascular destruction by the reticuloendothelial system. RBV monotherapy results in a decrease of approximately 2-3 gm/dL in hemoglobin levels within 4-8 weeks of treatment. Management involves RBV dose reductions/discontinuations beginning when the Hgb level reaches ≤10 mg/dL, blood transfusions and use of erythropoietin stimulating agents. In most cases, the anemia resolves within weeks following treatment cessation.

Subjects treated with RBV experienced more frequent and greater decreases in hemoglobin levels than those who did not receive RBV. The mean change from baseline in Hgb levels (at end of treatment) in subjects receiving a RBV-containing regimen was ~2.5 mg/dL, compared to <1.0 mg/dL for non-RBV or PBO-containing regimens. Decreases from baseline in hemoglobin levels were observed at Week 1 with further decreases observed through Week 3; from that point, values remained low for the duration of the treatment period, and by PTW 4 had typically returned to close to mean baseline values. The primary management for RBV-related hemoglobin decreases was RBV dose reductions.

- **Phase 2 Trials**

Across studies M11-652, M14-103 and M12-999:

- The mean decreases in hemoglobin levels from baseline to the end of treatment -2.5 mg/dL among subjects who received RBV and -0.6 mg/dL in those who did not receive RBV
- Nine percent and 2% of subjects had nadir Hgb levels <10.0 mg/dL and <8.0 mg/dL, respectively
- Twenty-eight percent of subjects treated with RBV underwent a RBV dose modification specifically for anemia and/or decreased hemoglobin

- One subject in the transplant trial interrupted RBV for 10 days due to dizziness and shortness of breath; RBV was resumed at a lower dose and the subject completed treatment
- Three subjects discontinued RBV due to: anemia with fatigue, CVA/sarcoma, and decreased creatinine clearance
- One subject with a Grade 2 Hgb value received a blood transfusion
- Five subjects received erythropoietin (all in the transplant study)
- Ninety-three percent of subjects who underwent a RBV dose modification achieved $SVR_{12}$.

- **Phase 3 Trials**

The mean change from baseline in Hgb levels in subjects treated with the 3-DAA + RBV regimen was -2.4 mg/dL, and for the PBO and 3-DAA alone groups it was ~-0.5 mg/dL. Decreases in Hgb levels occurred early in treatment (at TW 1) with further reductions through TW 3. From that point on, values remained low during the remainder of treatment and returned to baseline levels by PTW 4.

Grade 2 or higher decreases in hemoglobin levels occurred in 6.5% of subjects treated with 3-DAA + RBV compared to 0 in the 3-DAA and PBO groups, and only two subjects treated with 3-DAA + RBV had a Grade 4 Hgb.

Approximately 9% of females treated with 3-DAA + RBV had anemia compared to 6.6% of males. This may be a function of females generally starting treatment with lower Hgb levels as there was no difference in the mean reduction from baseline in Hgb levels between males and females.

The mean ($\pm$SD) age of subjects with anemia was 57.2 ($\pm$3.65) years for those without cirrhosis and 61.5 ($\pm$0.70) years for those with cirrhosis. In both groups, subjects with anemia were older than the mean for all subjects enrolled in the clinical trials: 54.32 ($\pm$3.78) years. More females, n=60, compared to males, n=40, had anemia and underwent a RBV dose modification. Over 95% of subjects were White. There was no difference in the number of days to RBV dose modification between subjects with and without cirrhosis: mean of 43.2 ($\pm$8.22) days in non-cirrhotics and mean of 40.5 ($\pm$4.94) days in cirrhotics.

Anemia/decreased hemoglobin were the two most frequently reported reasons for subjects to undergo a RBV dose modification. One-hundred subjects underwent RBV dose modifications due to anemia-related adverse events, and most events were graded as mild or moderate. The events leading to RBV dose modifications were primarily decreased hemoglobin/anemia, followed by anemia with fatigue, anemia with non-cardiac chest pain (also SAE), anemia with pallor, fatigue, dyspnea, anemia with dyspnea, exacerbation of coronary artery disease, mental fogginess with insomnia and irritability, and vomiting occurring in 1-3 subjects each.

Anemia was generally managed by RBV dose modifications. Three subjects received blood transfusions and five received erythropoietin. Very few subjects interrupted or discontinued RBV due to anemia and one subject temporarily interrupted DAAs due to anemia. Overall, 98% (98/100) of subjects who had a modification of their RBV dose due to anemia achieved $SVR_{12}$.

**Table 31 Anemia and anemia-management, Phase 3 trials**

| N (%) | 3-DAA + RBV x 12 weeks Non-cirrhotic N=1171 | 3-DAA x 12 weeks Non-cirrhotic N=509 | 3-DAA + RBV x 12 weeks Cirrhotic N=208 | 3-DAA + RBV x 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|
| Mean Hgb nadir (mg/dL) | -2.4 | -0.5 | -2.5 | -2.4 |
| ≥Grade 2 (<10.0 mg/dL) | 64 (5) | 0 | 12 (6) | 18 (10) |
| ≥Grade 3 (<8.0 mg/dL) | 3 (<1) | 0 | 2 (<1) | 1 (<1) |
| Grade 4 (<6.5 mg/dL) | 1 (<1) | 0 | 1 (<1) | 0 |
| AE listed as "anemia" | 71 (6) | 1 (<1) | 16 (8) | 18 (11) |
| RBV dose modification due to anemia-related events[1] | 65 (5.5) | 0 | 15 (7) | 20 (12) |
| RBC transfusion | 1 | 0 | 1 | 1 |
| Erythropoietin | 1 | 0 | 0 | 4 |

1 Includes: anemia, decreased hemoglobin, decreased RBCs, hemolytic anemia, and anemia with: pallor, dyspnea, increased creatinine, fatigue, non-cardiac chest pain, asthenia, anxiety, and/or dizziness

During OL treatment, the mean decrease from baseline in Hgb levels was -2.1 mg/dL; 14/252 had levels in the Grade 2 range and no subjects had a Grade 3 or 4 decrease. Events leading to RBV dose modifications included decreased hemoglobin/anemia (16), decreased hemoglobin/gout (1), right leg purpura/erythema nodosum/panniculitis (1), elevated bilirubin (1), diarrhea (1), rash with itching (1), and shortness of breath with dizziness (1).

The mean time to RBV dose reduction in the Compensated Cirrhosis trial was 37.5 days (range 8-76 days) in the 12-week arm and 43 days (9-141) in the 24-week arm.

***Reviewer comment: The addition of RBV to the 3-DAA regimen clearly increased the reduction from baseline in Hgb levels and the requirement for RBV dose modifications. In subjects with cirrhosis, the extended duration of treatment did not increase either the frequency or severity of ≥Grade 2 hemoglobin reductions or anemia-related adverse events. Extending duration of treatment to 24 weeks in cirrhotic subjects did not significantly increase the risk or severity of anemia. These data suggest the following: subjects receiving the 3-DAA regimen may not require the standard 1000/1200 mg WB RBV dose, RBV-associated anemia was not a serious complication of treatment, anemia was manageable with dose modification, and dose modifications did not negatively impact achievement of virologic response.***

**Skin and Skin Structures**

Rash and pruritus were observed in subjects treated with the 3-DAA regimen in Phase 2 and 3 trials. ABT-450 is an NS3/4 HCV protease inhibitor, and skin and skin structure adverse events have been reported in subjects treated with other approved protease inhibitors and RBV. In addition, RBV alone is associated with an increased frequency of rash and pruritus.

The Applicant conducted a special analysis to evaluate the potential for the 3-DAA regimen to cause significant adverse events in the skin and skin structure organ class. Rash-related adverse events were evaluated using a pre-specified (MedDRA) query (CMQ) and the severe

cutaneous reactions standardized MedDRA query (SMQ). The most frequently reported events were rash and pruritus.

- **Phase 2**

A total of 155 (27%) subjects in Study M11-652 experienced at least one treatment-emergent adverse event that met the drug-induced rash CMQ: 115 (26%) treatment-naïve and 40 (30%) prior null responders. The most common events in both treatment-naïve subjects and prior null responders were rash (11% treatment-naïve, 9% null responders), pruritus (13% treatment-naïve, 19% null responders). The overall frequency of events meeting this CMQ was numerically lowest in the group that did not receive RBV (Group E, 15%). One null responder subject had a treatment-emergent adverse event of generalized pruritus that led to discontinuation of study drug.

In Study M14-103, all 38 subjects received 3-DAA + RBV. Seven subjects had a rash (6) or pruritus event (1). Six events were considered mild, and one subject had a moderate facial rash which resolved with no intervention. There were no study drug interruptions or discontinuations.

- **Phase 3**

Table 32 shows the number of subjects with a drug-induced rash CMQ and the number of pruritus and rash events; note that many subjects had more than one event. There were no SAEs or severe cutaneous reactions, such as SJS, TEN, EM or DRESS. There were no preclinical signal for skin and skin structure toxicities and no photosensitivity was observed in a rat study. Of note, <1% of all study subjects experienced a photosensitivity reaction.

The frequency of rash and pruritus in the PBO group suggests a baseline for subjects with CHC who are not being treated. The frequencies between the PBO and 3-DAA alone groups suggest that the 3-DAA alone are not increasing the risk of these types of events. The comparison between non-cirrhotic subjects treated with the 3-DAA + RBV and 3-DAA alone suggest that the increased frequency of events may be attributable to the inclusion of RBV, as no other etiology could be identified. In cirrhotic subjects, puritus was more common and rash occurred with similar frequency as in non-cirrhotics.

The majority of events were graded as mild or moderate in severity and responded to treatment with topical or oral corticosteroids, oral antihistamines and/or other over-the-counter topical agents. Two subjects had a decrease in RBV dose due to pruritus, but no subject discontinued RBV or interrupted or discontinued the DAAs.

**Table 32 CMQ skin and skin structure events, Phase 3 trials**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic n=1171 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO* N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| Subjects with any CMQ event | 309 (26) | 70 (14) | 39 (15) | 77 (37) | 75 (44) |
| Pruritus events[1] | 135 (11.5) | 30 (6) | 11 (4) | 37 (18) | 34 (20) |
| Rash events[2] | 298 (25) | 34 (7) | 22 (9) | 38 (18) | 44 (26) |
| Other events | Stomatitis 8, scalp tenderness 1, | Stomatitis 4, impetigo 1, | Stomatitis 4, conjunctivitis | Stomatitis 3, conjunctivitis 1 | Stomatitis 1, conjunctivitis 1, |

| | | | | | |
|---|---|---|---|---|---|
| | conjunctivitis 1 | conjunctivitis 1 | 2, | | capillaritis 1 |

*During Double-Blind treatment period
1. Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized
2. Grouped term 'rash' included the following preferred terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, urticaria, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, erythema, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria

***Reviewer comment: The frequency of rash and pruritus were higher among subjects treated with RBV. In general the events were manageable with oral and topical medications, no subject discontinued study medications, and there were no severe cutaneous adverse reactions. Based on these data, a Warning is not necessary, and these data will be included in the Adverse Events section.***

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

When combined, the most common adverse events (TEAEs) reported by subjects treated with the 3-DAA alone compared to placebo was insomnia and when the 3-DAAs were co-administered with RBV, fatigue, headache, nausea, pruritus, insomnia, asthenia, dyspnea and rash were more frequently reported; all of these events are known to be related to RBV.

- **Phase 1 Trials**

Treatment-emergent adverse events experienced by ≥ 2.0% of subjects were headache (7%), diarrhea (4%), nausea and dizziness, (3% each), abdominal pain and constipation (2.5% each), and nasopharyngitis (2%).

- **Phase 2 Trials**

The large Phase 2 Study M11-652 provided an opportunity to assess the contribution of the individual DAAs and RBV to safety events. Among subjects who received a 3-DAA ± RBV regimen, the most commonly reported treatment-emergent adverse events having a reasonable possibility of being related to treatment were headache, fatigue, insomnia, diarrhea, asthenia, and pruritus. Table 33 shows the frequency of adverse events observed in ≥5% of subjects. All of these events were expected to occur, based on the known adverse event profile of each DAA and RBV, which were reported in the trial (see Section 5.3, Figure 1 for an explanation of each regimen).

Treatment naïve subjects in Groups F/G (with RBV) had ≥5% more anemia, nausea, fatigue, headache, insomnia, cough, dyspnea, pruritus and rash compared to Group E (no RBV).

All prior null responders were treated with RBV. With the exception of a slightly higher frequency of abdominal pain, diarrhea, arthralgia, and myalgia among prior null responders, the frequency and severity of all other adverse events were comparable between naïve and experienced subjects treated with RBV (Groups F/G compared to Groups K/L).

**Table 33 All grade TEAE events, by preferred term, reported by ≥5% of subjects in any group regardless of relatedness, Study M11-652**

| N (%) | A N=80 | B N=41 | C+D N=79 | E N=79 | F+G N=79 | H+I N=80 | Total Naïve N=438 | J N=45 | K+L N=45 | M+N N=43 | Total Nulls N=133 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anemia | 5 (6) | 1 (2) | 3 (4) | 1 (1) | 7 (9) | 6 (7.5) | 23 (5) | 3 (7) | 3 (7) | 2 (5) | 8 (6) |
| Abdominal pain | 1 (1) | 5 (12) | 9 (11) | 6 (8) | 7 (9) | 11 (14) | 39 (9) | 1 (2) | 7 (15) | 2 (5) | 10 (8) |
| Constipation | 3 (4) | 1 (2) | 5 (6) | 5 (6) | 1 (1) | 9 (11) | 24 (5.5) | 2 (4) | 1 (2) | 4 (9) | 7 (5) |
| Diarrhea | 8 (10) | 10 (24) | 8 (10) | 13 (16.5) | 10 (13) | 11 (14) | 60 (14) | 7 (16) | 8 (18) | 8 (19) | 23 (17) |
| Nausea | 12 (15) | 7 (17) | 16 (20) | 11 (14) | 19 (24) | 20 (25) | 85 (19) | 6 (13) | 9 (20) | 8 (19) | 23 (17) |
| Vomiting | 7 (9) | 4 (10) | 4 (5) | 4 (5) | 4 (5) | 4 (5) | 27 (6) | 4 (9) | 4 (9) | 3 (7) | 11 (8) |
| Asthenia | 7 (9) | 1 (2) | 8 (10) | 5 (6) | 3 (4) | 12 (15) | 36 (8) | 10 (22) | 4 (9) | 4 (9) | 18 (13.5) |
| Fatigue | 29 (36) | 13 (32) | 22 (28) | 16 (20) | 22 (28) | 30 (37.5) | 132 (30) | 12 (27) | 12 (27) | 9 (21) | 33 (25) |
| Irritability | 1 (1) | 4 (10) | 5 (6) | 5 (6) | 1 (1) | 10 (12.5) | 26 (6) | 7 (16) | 2 (4) | 3 (7) | 12 (9) |
| Arthralgia | 2 (2.5) | 2 (5) | 6 (8) | 7 (9) | 5 (6) | 9 (11) | 31 (7) | 3 (7) | 5 (11) | 7 (16) | 15 (11) |
| Myalgia | 4 (5) | 3 (7) | 5 (6) | 2 (2.5) | 3 (4) | 9 (11) | 26 (6) | 5 (11) | 4 (9) | 6 (14) | 15 (11) |
| Headache | 28 (35) | 13 (32) | 23 (29) | 15 (19) | 21 (27) | 28 (35) | 128 (29) | 15 (33) | 13 (29) | 14 (33) | 42 (32) |
| Insomnia | 10 (12) | 8 (20) | 9 (11) | 6 (8) | 16 (20) | 20 (25) | 69 (16) | 8 (18) | 6 (13) | 7 (16) | 21 (16) |
| Cough | 12 (15) | 5 (12) | 11 (14) | 2 (2) | 8 (10) | 12 (15) | 50 (11) | 7 (16) | 3 (7) | 9 (21) | 19 (14) |
| Dyspnea | 8 (10) | 3 (7) | 4 (5) | 1 (1) | 5 (6) | 8 (10) | 29 (7) | 4 (9) | 3 (7) | 3 (7) | 10 (7.5) |
| Pruritus | 14 (17) | 8 (20) | 8 (1) | 4 (5) | 10 (13) | 14 (18) | 58 (12) | 11 (24) | 7 (16) | 7 (16) | 25 (19) |
| Rash | 10 (12) | 2 (5) | 6 (8) | 6 (8) | 11 (14) | 15 (19) | 50 (11) | 2 (4) | 4 (9) | 6 (14) | 12 (9) |

***Reviewer comment: Based on the results of Study M11-652, it was expected that subjects treated with a regimen including the 3-DAA + RBV would experience the above listed adverse events, with the incidence of RBV-associated events (fatigue, insomnia, pruritus, cough, and asthenia) being higher in subjects who have RBV included in their regimen.***

Studies M14-103 and M12-999 were conducted in small subgroups of subjects that were treated with 3-DAA + RBV. Treatment-emergent adverse events were similar in type to those reported in subjects in Study M11-652 and the Phase 3 trials; however, the frequency of many events were higher among liver transplant recipients.

- **Phase 3 Trials**

The primary safety analysis was a comparison of adverse events between subjects treated with 3-DAA + RBV (with and without cirrhosis) compared to those treated with 3-DAA alone and those treated with PBO. A review of adverse events found the profile of events was comparable between treatment naïve and experienced subjects, and as such, the data was pooled by treatment regimen and duration of treatment. The most common (≥5%) adverse events reported in the Phase 3 trials are listed by treatment regimen in the Table 34.

In non-cirrhotic subjects, the data in the 3-DAA and PBO groups provide a direct comparison of natural history to active treatment and demonstrates that the 3-DAA appear to reduce the occurrence of some events and minimally increase others. It is notable that treatment with 3-

DAA did not alleviate fatigue, which is one of the most common complaints among HCV-infected patients. Nausea, pruritus, diarrhea, and asthenia occurred significantly more often in the 3-DAA + RBV groups; all of these events have been associated with treatment with RBV.

In cirrhotic subjects, fatigue was the only adverse event reported significantly more often in the 24 week arm. Dyspnea, rash and irritability numerically occurred with ≥5% frequency in the 3-DAA + RBV x 24-week arm compared to the 12-week arm. A comparison of the incidence of adverse events during the first 12 weeks of dosing demonstrated that only fatigue was more often reported in the 24-week arm, 44% versus 31%. After week 12, there was no clinically relevant increase in the frequency or severity of adverse events in the 24-week arm.

**Table 34 All grade TEAE, by preferred term, reported by ≥5% of subjects in any group regardless of relatedness, Phase 3 trials**

| N (%) | 3-DAA + RBV X 12 weeks Non-cirrhotic N=1171 | 3-DAA X 12 weeks Non-cirrhotic N=509 | PBO* N=255 | 3-DAA + RBV X 12 weeks Cirrhotic N=208 | 3-DAA + RBV X 24 weeks Cirrhotic N=172 |
|---|---|---|---|---|---|
| Fatigue | 383 (33) | 135 (27) | 67 (26) | 68 (33) | 80 (47) |
| Headache | 362 (31) | 129 (25) | 76 (30) | 58 (28) | 53 (31) |
| Nausea | 235 (20) | 43 (8) | 38 (15) | 37 (18) | 35 (20) |
| Pruritus[1] | 135 (12) | 30 (6) | 11 (4) | 37 (18) | 34 (20) |
| Dizziness | 83 (14) | 21 (4) | 11 (4) | 18 (9) | 10 (6) |
| Insomnia | 157 (13) | 26 (5) | 19 (8) | 32 (15) | 31 (18) |
| Asthenia | 140 (12) | 20 (4) | 17 (7) | 29 (14) | 22 (13) |
| Diarrhea | 139 (12) | 58 (11) | 23 (9) | 30 (14) | 29 (17) |
| Rash[2] | 298 (14) | 34 (7) | 22 (9) | 38 (18) | 44 (26) |
| Dyspnea[3] | 141 (12) | 11 (2) | 22 (9) | 25 (12) | 32 (19) |
| Abdominal pain[4] | 121 (10) | 35 (7) | 20 (8) | 28 (13) | 27 (16) |
| Cough | 94 (8) | 24 (5) | 13 (5) | 24 (12) | 19 (11) |
| Irritability | 54 (5) | 15 (3) | 12 (5) | 15 (7) | 21 (12) |
| Decreased appetite | 72 (6) | 15 (3) | 7 (3) | 12 (6) | 14 (8) |
| Dry skin | 62 (5) | 10 (2) | 4 (2) | 18 (9) | 11 (6) |
| Arthralgia | 60 (5) | 13 (3) | 16 (6) | 10 (5) | 14 (8) |
| Myalgia | 56 (5) | 14 (3) | 18 (7) | 9 (4) | 8 (5) |
| Vomiting | 50 (4) | 7 (1) | 6 (2) | 7 (3) | 14 (8) |

*During DB treatment period
1. Includes all CMQ terms, see Table 32
2. Includes all CMQ terms, see Table 32
3. Includes dyspnea and dyspnea on exertion
4. Includes abdominal discomfort, abdominal pain, abdominal pain upper and abdominal pain lower

During OL treatment in the PBO-controlled trials, the adverse event profile was similar with generally lower frequencies of fatigue (20%), headache (17%), nausea (14%), pruritus (10%), insomnia (12%), asthenia (9%), diarrhea (10%), dyspnea (9%), and rash (6%).

Overall, the majority of adverse events were mild in severity. Moderate and severe events are further discussed above in Section 7.3.4.

***Reviewer comment: Overall the 3-DAA + RBV and 3-DAA regimens were generally well tolerated with manageable adverse events. Adverse events that occurred at a frequency of at least 10% will be included in the label. There were more adverse events among subjects treated with RBV, and these were generally tolerable and manageable. Further, extending the duration of treatment from 12 to 24 weeks in cirrhotic subjects did not significantly increase the frequency of adverse events as the majority of events occurred during the initial 12 weeks of dosing.***

## 7.4.2 Laboratory Findings

Please see above for a discussion of ALT, bilirubin, alkaline phosphatase and hemoglobin abnormalities. The Applicant focused the assessment of laboratory abnormalities on those deemed "potentially clinically significant;" most of which met the threshold of being ≥Grade 3 abnormalities. No other laboratory parameters were identified that warranted special monitoring or management during treatment with the 3-DAAs.

**Hematology Parameters**

Changes in hemoglobin levels are discussed in Section 7.3.5.

In the Phase 2 trials, minimal numbers of subjects had abnormalities in platelet (2), low total white blood cell count (2), decreased neutrophil (4), increased eosinophils (0), or decreased lymphocyte (10) counts. No subjects had increased APTT or INR values.
In the Phase 3 trials, there were no Grade 3 or higher hematology abnormalities that occurred at >2% of study subjects, and besides hemoglobin levels, there are no other hematology abnormalities that require special monitoring. Of note, no subjects had a post-baseline increase in eosinophils >5 × $10^9$/L. Post-baseline ≥Grade 3 hematology abnormalities in the Phase 3 trials are shown in Tables 35, 36 and 37.

**Table 35 ≥Grade 3 hematology abnormalities, PBO-Controlled Trials**

| N (%) | 3-DAA + RBV N=770 | PBO[1] N=255 |
|---|---|---|
| Platelets (<50 x $10^9$/L) | 0 | 0 |
| WBC count (>20 x $10^9$/L) | 8 (1) | 0 |
| WBC count (<2 × $10^9$/L) | 0 | 0 |
| Total neutrophils (<1 × $10^9$/L) | 1 (<1) | 2 (<1) |
| Lymphocytes (<0.5 × $10^9$/L) | 1 (<1) | 0 |
| APTT (>2 × ULN) | 6 (<1) | 0 |
| INR (>2 × ULN) | 4 (<1) | 2 (<1) |

1. During Double-Blind treatment period

**Table 36 ≥Grade 3 hematology abnormalities, Regimen-Controlled Trials**

| N (%) | 3-DAA + RBV N=401 | 3-DAA N=509 |
|---|---|---|
| Platelets (<50 x $10^9$/L) | 0 | 1 (1) |
| WBC count (>20 x $10^9$/L) | 1 (<1) | 0 |
| WBC count (<2 × $10^9$/L) | 2 (<1) | 0 |
| Total neutrophils (<1 × $10^9$/L) | 2 (<1) | 1 (<1) |
| Lymphocytes (<0.5 × $10^9$/L) | 1 (<1) | 0 |
| APTT (>2 × ULN) | 0 | 1 (<1) |
| INR (>2 × ULN) | 1 (<1) | 5 (1) |

**Table 37 >Grade 3 hematology abnormalities, Compensated-Cirrhosis Trial**

| N (%) | 3-DAA + RBV X 12 weeks N=208 | 3-DAA + RBV X 24 weeks N=172 |
|---|---|---|
| Platelets (<50 x $10^9$/L) | 2 (1) | 0 |
| WBC count (>20 x $10^9$/L) | 1 (<1) | 0 |
| WBC count (<2 × $10^9$/L) | 3 (1) | 1 (<1) |
| Total neutrophils (<1 × $10^9$/L) | 1 (<1) | 3 (2) |
| Lymphocytes (<0.5 × $10^9$/L) | 5 (2) | 3 (2) |
| APTT (>2 × ULN) | 1 (<1) | 1 (1) |
| INR (>2 × ULN) | 1 (<1) | 1 (1) |

**Other Chemistry Parameters**

Transaminase and bilirubin elevations are discussed in Section 7.3.5.

In the Phase 2 and 3 trials, there was very few potentially clinically significant chemistry abnormalities reported. In the Phase 3 Compensated Cirrhosis trial, only elevated glucose levels were reported more often in subjects treated for 24 weeks; most were single abnormalities and there were no clinical events associated with these increases. For the other parameters, most abnormalities were isolated values that were within normal limits on retest. There are no additional chemistry parameters that warrant monitoring for in clinical practice.

**Table 38 >Grade 3 chemistry abnormalities, Placebo-Controlled Trials**

| N (%) | 3-DAA + RBV N=770 | PBO[1] N=255 |
|---|---|---|
| Elevated creatinine | 2 (<1) | 0 |
| Decreased CrCl | 1 (<1) | 0 |
| Elevated uric acid | 5 (<1) | 0 |
| Calcium<br>-High<br>-Low | <br>0<br>3 (<1) | <br>0<br>1 (<1) |
| Magnesium<br>-High | <br>3 (<1) | <br>0 |
| Sodium<br>-Low | <br>6(<1) | <br>1 (<1) |
| Potassium<br>-High<br>-Low | <br>0<br>1 (<1) | <br>2 (<1)<br>1 (<1) |
| Glucose<br>-High | <br>6 (<1) | <br>1 (<1) |
| Elevated trigylcerides | 15 (2) | 3 (1) |

1. During Double-Blind treatment period

**Table 39 >Grade 3 chemistry abnormalities, Regimen-Controlled Trials**

| N (%) | 3-DAA + RBV N=401 | 3-DAA N=509 |
|---|---|---|
| Elevated creatinine | 1 (<1) | 0 |
| Decreased CrCl | 1 (<1) | 0 |
| Elevated uric acid | 1 (<1) | 0 |
| Calcium<br>-Low | <br>1 (<1) | <br>1 (<1) |
| Magnesium<br>-High | <br>1 (<1) | <br>0 |

| | | |
|---|---|---|
| Sodium<br>-Low | 1 (<1) | 6 (1) |
| Potassium<br>-Low | 0 | 1 (<1) |
| Glucose<br>-High | 2 (<1) | 1 (<1) |
| Elevated trigylcerides | 2 (<1) | 7 (1) |

**Table 40 >Grade 3 chemistry abnormalities, Compensated-Cirrhosis Trial**

| N (%) | 3-DAA + RBV<br>X 12 weeks<br>N=208 | 3-DAA + RBV<br>X 24 weeks<br>N=172 |
|---|---|---|
| Elevated creatinine | 1 (<1) | 2 (1) |
| Decreased CrCl | 1 (<1) | 3 (2) |
| Elevated uric acid | 5 (2) | 6 (3) |
| Calcium<br>-High | 1 (<1) | 1 (<1) |
| Sodium<br>-Low | 2 (1) | 1 (<1) |
| Potassium<br>-Low | 1 (<1) | 1 (<1) |
| Glucose<br>-High | 4 (2) | 12 (7) |
| Elevated trigylcerides | 0 | 3 (2) |

### 7.4.3 Vital Signs

There were no patterns or differences in vital signs observed in any of the clinical trials.

### 7.4.4 Electrocardiograms (ECGs)

In clinical trials, there were no significant changes in the ECGs of subjects treated with the 3-DAAs ± RBV.

The Applicant conducted a Thorough QT (TQT) study (Study M12-680) that demonstrated the 3-DAA regimen did not meet the threshold for QTcF prolongation based on ICH E14 guidelines at therapeutic or supratherapeutic doses.

### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were required or conducted.

### 7.4.6 Immunogenicity

ABT-450, ombitasvir and dasabuvir are not immunogenic.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

As discussed above, exposures associated with doses of paritaprevir >150 mg/day were associated with more frequent elevations of transaminase and bilirubin levels, and doses of dasabuvir >400 bid were associated with a higher frequency of low hemoglobin and hematocrit levels.

### 7.5.2 Time Dependency for Adverse Events

Adverse events occurred at all times during dosing with the 3-DAAs either with or without RBV. Hyperbilirubinemia, transaminitis, and anemia occurred early in treatment, typically within the first 1-4 weeks of dosing, generally stabilized and returned toward baseline levels by end of treatment or soon after (by PTW4).

### 7.5.3 Drug-Demographic Interactions

None

### 7.5.4 Drug-Disease Interactions

None

### 7.5.5 Drug-Drug Interactions

A substantial number of drug-drug interaction studies were conducted. Based on these studies, the following recommendations about concomitant medications will be included in the label:

The following drugs will specifically be contraindicated for co-administration with Viekira Pak:

- alfuzosin HCL
- phenytoin, phenobarbital, carbamazepine
- efavirenz
- ergotamine, dihydroergotamine, ergonovine
- methylergonovine
- gemfibrozil, lovastatin, simvastatin
- oral midazolam, triazolam
- pimozide
- rifampin
- salmeterol
- St. John's Wort (*Hypericum perforatum*)
- sildenafil (when used for the treatment of pulmonary arterial hypertension)

In general, use of a medication contraindicated with DAA administration can be stopped 1-2 weeks prior to treatment and restarted 1-2 weeks following completion of treatment.

**Fluticazone and other glucocorticoids metabolized by CYP3A4:** Co-administration is not recommended due to risk of Cushing's syndrome and adrenal suppression reported with ritonavir-containing regimens.

**Antiretroviral Agents:**

- Co-administration of efavirenz with the 3-DAAs is contraindicated due to poor tolerability.
- Lopinavir will be contraindicated for co-administration due to concerns about potential overlapping gastrointestinal adverse events and hepatotoxicity for ABT-450 and lopinavir, and the potential for resistance should any safety issues lead to premature discontinuation of either component of HIV or HCV therapy.
- Darunavir is not recommended due to reduced darunavir $C_{trough}$ level and a complicated dosing strategy (i.e., stopping ritonavir for the anti-HIV-1 regimen and re-starting when the anti-HCV regimen is stopped), which raise concerns about loss of anti-HIV-1 suppression; a pilot trial investigating different darunavir regimens is ongoing.
- Rilpivirine is not recommended because steady-state exposures of rilpivirine were increased significantly (approximately 100% to 300% increase in $C_{max}$, $AUC_{24}$ and $C_{trough}$) following co-administration with the 3-DAA regimen, regardless of administration schedule.
- Atazanavir/rtv (evening) is not recommended due to increased ABT-450 exposures

Antiretroviral agents for which co-administration with the 3-DAAs would be reasonable include tenofovir, lamivudine, emtricitabine, raltegravir and atazanavir (morning).

**Opiate Substitution agents:** No dose adjustment is required during co-administration of methadone with the 3-DAAs. Further, the results of the clinical trial (Study M14-103) demonstrate that buprenorphine, methadone and naloxone can be safely co-administered with the 3-DAAs.

**Immunosuppressants:** Subjects on cyclosporine (CsA) who start ABT 450/r with ombitasvir and/or dasabuvir should reduce their total daily CsA dose to one-fifth of the pre-DAA dose and CsA should be administered once daily. For tacrolimus, it will be recommended that the dose be reduced to 0.5 mg/week. For both agents, subsequent dose and dosing frequency modifications should be further informed by the individual drug level data. No dose modifications for ABT-450, ritonavir, ombitasvir or dasabuvir are required when co-dosing with cyclosporine or tacrolimus.

In Study M12-999, no subject had a cyclosporine level below the reference range or >225.0 ng/mL. Seven subjects had elevated tacrolimus levels; 5 on treatment and 2 post-treatment. No subject had a neurologic adverse event or hypertension associated with elevated tacrolimus levels. Two subjects with elevated tacrolimus levels also had elevations of their serum creatinine; one subject was still taking the twice-daily pre-study dose. Eight subjects had one or more low tacrolimus levels; all were during the post-treatment period and six were isolated occurrences. All levels returned to the therapeutic range during follow-up and there were no events of rejection.

**Estrogen containing oral contraceptives**: Due to excessive transaminitis, estrogen-containing oral contraceptives were excluded from use in the Phase 3 trials. A drug-drug interaction study with ethinyl estradiol/norgestimate being conducted in healthy volunteers was paused due to increased ALT levels in the first six of seven subjects. Pharmacokinetic data demonstrated significantly lower $AUC_{24}$ and $C_{max}$ for ABT-450, ritonavir, and ABT-333. The Applicant amended the study to add an evaluation of a low dose progestin only oral contraceptive. The results from this arm demonstrated no significant impact on the pharmacokinetics of any of the DAAs or

progestin. Based on these results, the Applicant added a fourth arm in which a NET/EE combination product was evaluated; 9/12 subjects had ALT elevations and dosing was discontinued.

***Reviewer comment: Although the DAAs do not appear to negatively impact fetal development, RBV is a teratogen, and steps to avoid pregnancy during RBV dosing and for six months post-dosing are required. In many populations, RBV will be co-administered with the DAAs and adequate forms of contraception are required during the dosing period. Therefore, women of child bearing potential, who are not surgically sterile, will be instructed to use at least 2 effective methods of contraception; however, due to excessive ALT elevations, caution related to use of estrogen-containing oral contraceptives and monitoring of liver functions will be detailed in the labeling.***

**Pravastatin and Rosuvastatin:** The concentration of both drugs was increased. The dose of pravastatin should not exceed 10 mg, and rosuvastatin 40 mg.

**Ketoconazole:** Doses of ketoconazole >200 mg/day are not recommended.

**Furosemide:** Furosemide $C_{max}$ was increased by ~50%. Clinical monitoring of patients is recommended and a decrease in dose up to 50% can be considered based on clinical response.

**Carbamazepine**: Co-administration of carbamazepine resulted in decreased exposures of the DAAs to an extent that could result in reduced antiviral activity. In addition, 2 subjects experienced elevations of ALT, one to Grade 3 and the other to Grade 2. As such, co-administration of carbamazepine with 3-DAAs will not be recommended.

**Alprazolam:** The concentration of alprazolam was increased. Clinical monitoring of patients is recommended and a decrease in alprazolam dose can be considered based on clinical response.

**Digoxin and Warfarin:** No dose adjustment is required.

**Omeprazole:** No dose adjustments are necessary when the DAAs are co-administered with pH elevating agents or inhibitors of CYP2C19.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

None of the DAAs demonstrated mutagenic or carcinogenic potential in vitro. Two cases of hepatocellular carcinoma occurred in subjects with cirrhosis. Hepatocellular carcinoma is a very slow growing tumor and is associated with long-standing HCV infection. Based on the timing of the diagnosis of these cancers, it is highly unlikely that they could be considered treatment related.

## 7.6.2 Human Reproduction and Pregnancy Data

Viekira Pak™ (the 3-DAAs co-packaged together) will be labeled as Pregnancy Category B.

RBV is Pregnancy Category X because it can cause significant teratogenic and/or embryocidal effects. Females of childbearing potential ensure they use adequate forms of birth control while receiving RBV, and for at least 6 months after stopping RBV. Females are to have negative results for pregnancy tests performed prior to treatment. Males are to be abstinent from sexual intercourse, surgically sterile or agree to practice two effective forms of birth control throughout RBV dosing and for 6 months after the last dose of study drug.

As discussed in Section 7.3.5 above, during the conduct of the Phase 3 studies use of estrogen-containing hormonal contraceptives was disallowed.

Eleven pregnancies were reported in the 3-DAA development program and are summarized below.

**Phase 1 Studies**

In Study M11-389:

- Subject 112 who received ABT-450/r/ABT-267 was discontinued from the study due to a positive pregnancy result. The subject gave birth to a healthy male baby with no complications or birth defects.

In Study M13-782:

- Subject 312 had a spontaneous abortion (occurring within 12 weeks of gestation) 25 days after the last dose of study drug (ABT-450/r + ABT-267 + ABT-333 in Period 1, ABT-450/r + ABT-267 + ABT-333 and rilpivirine 25 mg QD in Period 2). The event was assessed by the investigator as having a reasonable possibility of being related to DAA treatment and to rilpivirine.

**Phase 2 Studies**

In Study M11-652:

- Subject 8114 who received 3-DAA + RBV for 12 weeks had a positive urine pregnancy test at the PTW 24 visit and gave birth to a healthy male baby with no birth defects.
- Subject 8149 who received 3-DAA + RBV for 12 weeks became pregnant after her PTW 24 visit and had a spontaneous abortion at approximately 9 weeks' gestation. The spontaneous abortion was assessed by the investigator as being not related to DAA or RBV (updated pregnancy since the original NDA submission).

In Study M12-746:

- Subject 2556 who received ABT 450/r + ABT-333 + RBV reported becoming pregnant approximately 8 months after the last dose of study drugs and gave birth to a healthy female baby with no complications or birth defects.

**Phase 3 Trials**

In Study M11-646:

- Subject 407212 had a positive urine pregnancy test at the PTW 8 visit and delivered a healthy male infant without complications or birth defects.
- Subject 600208 had a positive pregnancy test on PTD 120 and had an elective abortion on PTD 140.
- Subject 462208 was reported to be pregnant on PTD 190; however, no further information regarding this pregnancy outcome was provided due to local privacy laws.

In Study M13-961:

- Subject 237511 in the 3-DAA treatment group had a spontaneous abortion (at approximately 8 weeks of gestation) on PTD 137. This event was assessed by the investigator as having a reasonable possibility of being related to DAA treatment.

In Study M14-002:

- Subject 104406 in the 3-DAA treatment group reported becoming pregnant on PTD 162 and had an elective abortion on PTD 171.

In Study M13-389:

- Subject 10039 in the 3-DAA + RBV for 12 weeks group became pregnant after her PTW 24 visit and is expected to deliver in December 2014 (new pregnancy since the database lock for the NDA submission).

***Reviewer comment: It does not appear that the 3-DAA increase the risk of adverse pregnancy outcomes.***

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No studies in the pediatric population have been conducted. A Proposed Pediatric Study Plan (PPSP) was submitted and reviewed by DAVP and the PERC. An agreed upon PSP dated November 19, 2013, provides for a program of formulation development, clinical pharmacology and clinical trials. Final study reports will be submitted by August 2019.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Extensive testing was undertaken, including quantitative whole body autoradiography in rodents to determine CNS penetration, in vitro receptor binding studies to identify potential off-target effects, s standard battery of CNS/neurobehavioral safety pharmacology studies in rodents, and adverse events related to abuse potential were assessed in placebo-controlled clinical studies. Based on the findings from these investigations, none of the DAAs have abuse potential (see also the Pharmacology/Toxicology review).

## 7.7 Additional Submissions / Safety Issues

A 120-day safety update was submitted and reviewed. There were no new data included in the safety update that changed the overall assessment of safety of the 3-DAAs. The update

included data from the six Phase 3 trials and Study M14-103, which were ongoing with all subjects in post-treatment follow-up. Salient findings include:

- Two additional deaths, both occurring during off-treatment follow-up: Subject 141106 in Study M13-099 died 278 days after the last dose of study drugs due to esophageal varices hemorrhage, and Subject 149401 in Study M14-002 died 208 days after the last dose of study drugs due to brain injury and grand mal convulsions.
- Subject 600101 in Study M13-099 was a 28 year old female with a SAE of esophageal varices hemorrhage on day 398 (approximately 32 weeks after completing study drugs).

I

***Reviewer comment: One subject in the Compensated Cirrhosis trial died and two had SAEs related to esophageal varices bleeding, and two subjects were diagnosed with hepatocellular carcinoma. These subjects all had complications of chronic hepatitis, which suggests that there remains a risk for liver related morbidity and mortality even with successful treatment. It will be interesting to see if there are more events observed in the ongoing long-term follow-up studies.***

# 8 Postmarket Experience

None of the DAAs are approved elsewhere in the world. As such, there are no post-marketing experience data available.

# 9 Appendices

## 9.1 Literature Review/References

All of the Phase 3 clinical trials reviewed in this NDA have been either published in peer-reviewed journals or presented in public venues.

## 9.2 Labeling Recommendations

In this section, major issues regarding the Applicants' proposed labeling language (unbolded font) and DAVP's proposed changes and additions (bolded font) are discussed. Labeling discussions are continuing and additional edits to the labeling will occur after this Clinical Review is due to be archived, and will be further summarized in the CDTL and DD memos.

- The Applicants' proposed Indication and Usage statement read:

(b) (4)

The Applicants' proposed recommendations for treatment regimen and duration are shown in the following table.

| Patient Population | Treatment | Duration |
|---|---|---|
| (b) (4) | | |

(b) (4)

**DAVP was unable to identify specific subgroups of patients for whom co-administration of RBV was not beneficial in reducing the virologic failure rate, and will recommend that all GT1a treatment naïve non-cirrhotic patients receive 12 weeks of 3-DAA + RBV. Specifically, the data in non-cirrhotic GT1a treatment naïve subjects suggests that RBV is an important component necessary to reduce virologic failure (and presumably treatment-emergent resistance), especially in subjects with non-CC IL28b genotypes. An argument could be made that GT1a subjects with the CC genotype could be treated with the 3-DAA alone regimen as there was a small difference in response rates between regimens. However, this would require pre-treatment IL28B genotype testing, which may not be universally available and would likely require use of unapproved assays. Although the risk of virologic failure is relatively low when RBV is not co-administered, for those subjects who fail with resistance substitutions in multiple DAA targets there are currently no ideal retreatment choices, and any retreatment regimen would likely involve use of a pegIFN/RBV-based regimen, or the patient may have to delay re-treatment until newer agents become available. There were more RBV-associated adverse events such as anemia, pruritus and skin rash, and bilirubin elevations; however, these events were generally tolerable and manageable.**

**This reviewer recommends that all GT1a cirrhotic subjects be treated with 24 weeks of 3-DAA + RBV, again to reduce the risk of relapse. Extending the duration of 3-DAA + RBV treatment by 12 weeks appeared to decrease the virologic failure rate by nearly 50% in all subgroups of GT1a-infected subjects. Extending treatment was associated with an increase in the frequency of certain adverse events, but they were generally mild to moderate, manageable, and there were no clinically relevant differences in SAEs or discontinuations due to adverse events.**

(b) (4)

**Two limitations of use will be included: the recommendation that the 3-DAAs not be used in patients with moderate or severe hepatic impairment, and that there are no data on use of the 3-DAA in patients who failed to respond to DAA treatment.**

- The Applicant proposed (b) (4)

**Subsequent to submission of the NDA, the Applicant proposed** (b) (4) **and if discontinued prior to treatment they could be restarted approximately 2 weeks after treatment has completed. A final decision will be made at a later date.**

- The Applicant proposed (b) (4)

**Information conveying the risks and management of transaminitis will likely be included in the Warnings and Precautions and Adverse Event sections of the label.**

- Section 14.1, Clinical Trials, presented a substantial amount of irrelevant clinical data

**This section will be pared down to be more concise. For example, (b) (4) will be deleted as will the statements presenting (b) (4) (b) (4) will be deleted as it provides redundant information.**

- The Applicant proposed to include a Patient Package Insert (PPI) to provide information to patients on the safe use of the 3-DAA ± RBV regimen.

**Although there is no need for a Risk Evaluation and Mitigation Strategy (REMS), it was determined that due to: (1) the known risk of teratogenicity related to a ribavirin-containing regimen and the need for effective contraception, and (2) hepatotoxicity with or without concomitant administration of estrogen-containing therapies with the 3-DAA combination, that a Medication Guide would be necessary to help mitigate potential risk.**

## 9.3 Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application as there were no review issues that required outside advice or opinions.

## 9.4 Clinical Investigator Financial Disclosure Review

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes X | No ☐ (Request list from applicant) |
| Total number of investigators identified: 300 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 10<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in sponsor of covered study: 0 | | |

| | | |
|---|---|---|
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes X | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes X | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from applicant) |

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There were no interests/arrangements or investigators who are sponsor employees that raise questions about the integrity of the data.

Specifically, the Applicant took steps to minimize potential bias of clinical investigators from financial interests and arrangements by utilizing randomized study designs with no site enrolling numbers of subjects so high as to influence results. The primary endpoint for all of the covered studies included an objective laboratory endpoint of HCV RNA. In addition the Phase 3 studies also utilized an independent Data Safety Monitoring Board (DSMB) and an Independent Hepatic Expert Panel for impartial monitoring of safety.

In summary, the disclosed financial interests/arrangements did not appear to affect the approvability of this application.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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RUSSELL D FLEISCHER
09/18/2014

LINDA L LEWIS
09/18/2014
I concur with the clinical reviewer's conclusions regarding approval of Viekira Pak.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 206619** **Applicant: AbbVie** **Stamp Date: 04/21/2014**

**Drug Names: ABT-450/r, ombatasvir, dasabuvir** **NDA Type: Priority**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | X | | | |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). | (b)(1) | | | |
| **505(b)(2) Applications** | | | | | |
| 13. | If appropriate, what is the reference drug? | | | X | |
| 14. | Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature? | | | X | |
| 15. | Describe the scientific bridge (e.g., BA/BE studies) | | | X | |
| **DOSE** | | | | | |
| 16. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: There are 17 Phase 1 and 2 studies that were used to determine appropriate dose and duration of the DAA combination. | X | | | |
| **EFFICACY** | | | | | |
| 17. | Do there appear to be the requisite number of adequate and well-controlled studies in the application? | X | | | |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | The Applicant submitted 6 pivotal Phase 3 trials to support the proposed indication of ABT-450/r/ABT-267 and ABT-333 are indicated for the treatment of GT1 chronic hepatitis C infection, including in patients with cirrhosis. | | | | |
| 18. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 19. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 20. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | X | | | |
| **SAFETY** | | | | | |
| 21. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 22. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | X | | | |
| 23. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 24. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | | | X | |
| 25. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | X | | | |
| 26. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 27. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 28. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| **OTHER STUDIES** | | | | | |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| 29. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | |
| 30. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | X | |
| **PEDIATRIC USE** | | | | | |
| 31. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| **ABUSE LIABILITY** | | | | | |
| 32. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | X | | | |
| **FOREIGN STUDIES** | | | | | |
| 33. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | X | | | |
| **DATASETS** | | | | | |
| 34. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 35. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 36. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 37. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 38. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| **CASE REPORT FORMS** | | | | | |
| 39. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 40. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | X | | | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 41. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 42. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____X____**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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|---|---|
| Russell Fleischer, PA-C, MPH | May 22, 2014 |
| Reviewing Medical Officer | Date |
| Linda L. Lewis, MD | May 22, 2014 |
| Clinical Team Leader | Date |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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RUSSELL D FLEISCHER
05/29/2014

LINDA L LEWIS
05/29/2014