Hematologic Analysis of Paritaprevir(ABT-450)/r/Ombitasvir and Dasabuvir + RBV in TURQUOISE-I

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BACKGROUND

- Combination therapy of ribavirin (RBV) and peginterferon (pegIFN) with protease inhibitors for the treatment of HCV is commonly associated with hematologic abnormalities
- An IFN-free oral regimen for treatment of HCV that combines 3 direct-acting antiviral agents (3D) ±RBV has been studied in phase 3 trials. The multi-targeted 3D regimen includes:
  - Ombitasvir, an NS5A inhibitor
  - Paritaprevir (formerly ABT-450), an HCV NS3/4A protease inhibitor identified by AbbVie and Enanta as a lead compound for clinical development
    - Co-administered with low-dose ritonavir (r) to increase peak, trough, and overall exposures of paritaprevir
  - Dasabuvir, an NS5B non-nucleoside RNA polymerase inhibitor
  - Ombitasvir and paritaprevir/r are co-formulated
  - Extensive phase 1 drug–drug interaction studies in healthy volunteers with tenofovir, emtricitabine, atazanavir, and raltegravir indicated no clinically meaningful alterations in HCV or HIV drug exposures[1,2]
- The 3D regimen, ±RBV, has been studied in >2700 HCV genotype (GT) 1-infected patients to date
  - SVR12 rates achieved with 3D + RBV in patients with GT1 infection within the phase 3 program were:
    - ≥96% SVR12 in non-cirrhotic treatment-naïve and treatment-experienced patients after 12 weeks of treatment, regardless of subtype (ie, 1a vs 1b)[3–6]
    - 92% and 97% SVR12 for 12- and 24-week treatment, respectively, in treatment-naïve and treatment-experienced patients with cirrhosis[7]
- TURQUOISE-I is a multicenter, phase 2/3 study assessing the safety and efficacy of 3D + RBV for 12 or 24 weeks in HCV GT1/HIV-1 co-infected patients, including those with cirrhosis
  - In TURQUOISE-I part 1a, the phase 2 pilot cohort, 29/31 patients (94%) receiving 3D + RBV for 12 weeks and 29/32 patients (91%) receiving 3D + RBV for 24 weeks achieved SVR12. Two of the patients in the 24-week arm who did not achieve SVR12 had recurrence of viremia due to HCV re-infection

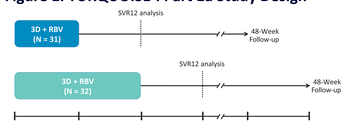
OBJECTIVE

- We analyzed immune parameters in patients co-infected with HCV and HIV-1 treated with the 3D + RBV regimen in part 1a of the TURQUOISE-I study

METHODS

- TURQUOISE-I is an ongoing, randomized, open-label phase 2/3 study
- Part 1a and 1b: phase 2 pilot cohort; part 2: phase 3 cohort. Results from part 1a are presented here

Figure 1. TURQUOISE-I Part 1a Study Design



All patients will be followed for 48 weeks after HCV treatment end.
3D: co-formulated paritaprevir/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID.
RBV: 1000 or 1200 mg daily according to body weight in 2 divided doses (<75 kg and ≥75 kg, respectively).

METHODS (CONTINUED)

KEY ELIGIBILITY CRITERIA

- 18–70 years of age
- Body mass index ≥18 and <38 kg/m^2
- HCV GT1 infection (plasma HCV RNA >10 000 IU/mL)
- HCV treatment-naïve or pegIFN/RBV-experienced
  - For pegIFN/RBV-experienced, prior relapse,* partial response,† or null response‡
- Cirrhosis with Child-Pugh score of A or absence of cirrhosis
- HIV-1 RNA <40 copies/mL and CD4+ count ≥200 cells/mm^3 or CD4+% ≥14%
- Stable atazanavir- or raltegravir-inclusive ART regimen

*Relapse: HCV RNA undetectable at or after the end of treatment but with a detectable level within 52 weeks thereafter.
†Partial response: ≥2 $\log_{10}$ IU/mL HCV RNA reduction at treatment week 12 but detectable at the end of treatment.
‡Null response: <2 $\log_{10}$ IU/mL HCV RNA reduction at treatment week 12 or <1 $\log_{10}$ IU/mL HCV RNA reduction at treatment week 4.

ANALYSIS OF HEMATOLOGIC PARAMETERS

- Laboratory values were assessed at every on-treatment and post-treatment visit
- Treatment-emergent adverse events (AEs) were assessed from the first dose until 30 days after the last dose for any patient who received at least 1 dose of study drugs

RESULTS

- In TURQUOISE-I part 1a, 19% of patients in each arm had cirrhosis, 78%–84% had IL28B non-CC genotype, and 16% in each arm had a null response to prior pegIFN/RBV therapy **(Table 1)**

Table 1. Baseline Demographic and Disease Characteristics in TURQUOISE-I Part 1a

	12-Week Arm (N = 31)	24-Week Arm (N = 32)
Male, *n* (%)	29 (94)	29 (91)
Black, *n* (%)	7 (23)	8 (25)
Age, mean ± SD	50.9 ± 6.0	50.9 ± 8.3
Cirrhosis, n (%)	6 (19)	6 (19)
IL28B non-CC genotype, n (%)	26 (84)	25 (78)
HCV genotype 1a, n (%)	27 (87)	29 (91)
HCV RNA ($\log_{10}$ IU/mL), mean ± SD	6.54 ± 0.57	6.60 ± 0.78
Prior HCV treatment history, n (%)		
Treatment-naive	20 (65)	22 (69)
PegIFN/RBV treatment-experienced	11 (35)	10 (31)
Relapser	1 (3)	3 (9)
Partial responder	5 (16)	2 (6)
Null responder	5 (16)	5 (16)
Hemoglobin (g/dL), mean	15.3	15.2
Platelet count (x10^9/L), mean	202.9	210.7
CD4+ T-cell count (/mm^3), n (%)		
<200	0	1 (3)
200–<350	2 (6)	4 (13)
350–<500	8 (26)	8 (25)
≥500	21 (68)	19 (59)
Atazanavir HIV-1 ART regimen, n (%)	16 (52)	12 (37)
Raltegravir HIV-1 ART regimen, n (%)	15 (48)	20 (63)

RESULTS (CONTINUED)

HEMOGLOBIN

- Treatment-emergent anemia was reported in 1 patient in the 12-week arm (3%) and in 3 patients in the 24-week arm (9%). There was no difference in the rate of anemia according to treatment duration (*P* >.1)
- No patient in either treatment group had a grade 3 or 4 decline in hemoglobin **(Table 2)**
- Hemoglobin decreases were comparable between 12- and 24-week treatment arms **(Figure 2)**
- For patients in the 12-week arm, the mean (SD) hemoglobin decrease was -2.54 (1.536) g/dL and the median (range) was -2.55 (-6.10, -0.40) g/dL at treatment week 12. For patients in the 24-week arm, mean (SD) was -2.50 (1.647) g/dL and median (range) was -2.30 (-5.60, 0.80) at treatment week 24. Hemoglobin levels returned to near baseline levels after treatment
- Longer treatment duration was not associated with a higher rate of RBV dose modification due to decreased hemoglobin. Four patients in the 12-week arm (13%) and 2 in the 24-week arm (6%) had a modification of RBV dose due to hemoglobin declines
  - All of these patients achieved SVR12
  - The lowest dose of RBV among these patients was 400 mg. Reductions of RBV dose to 600–800 mg were most common
  - Hemoglobin levels stabilized with RBV dose modification in these patients
- No patient was administered erythropoietin or received a blood transfusion
- Reticulocyte counts increased throughout the treatment period in patients in each arm **(Figure 3)**

Table 2. Hemoglobin Declines by Grade

	12-Week Arm (N = 31)	24-Week Arm (N = 32)
Hemoglobin decline, n (%)		
Grade 1 (LLN to 10 g/dL)	14 (45.2)	18 (56.3)
Grade 2 (<10 to 8 g/dL)	4 (12.9)	3 (9.4)
Grade 3 (<8 to 6.5 g/dL)	0	0
Grade 4 (<6.5 g/dL)	0	0

LLN, lower limit of normal.

Figure 2. Mean Change From Baseline in Hemoglobin

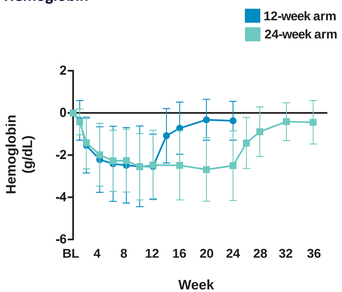
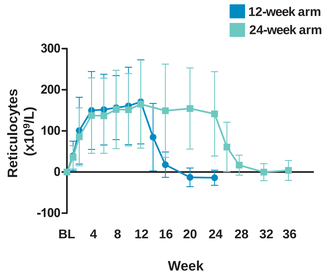


Figure 3. Mean Change From Baseline in Reticulocytes



CD4+ T-CELLS

- Mean absolute CD4+ T-cell counts and lymphocytes decreased during treatment and increased to above baseline levels by post-treatment week 12 **(Figure 4)**
- CD4+ T-cell percentages and white blood cell counts remained stable over time in both treatment arms **(Figure 5)**
- There were 3 patients who experienced a CD4+ T-cell count <200 cells/mm^3 or CD4+ percentage <14% during treatment. None experienced an AIDS-associated opportunistic infection

Figure 4. Mean Change From Baseline in CD4+ T-cell Count and Lymphocyte Count

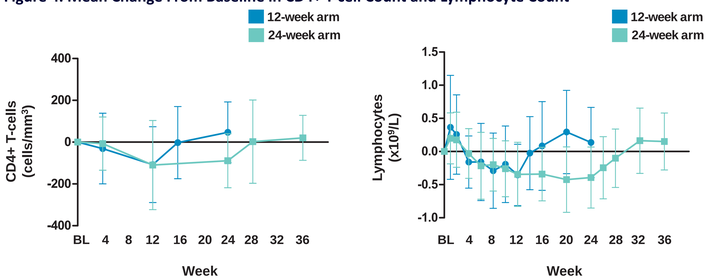
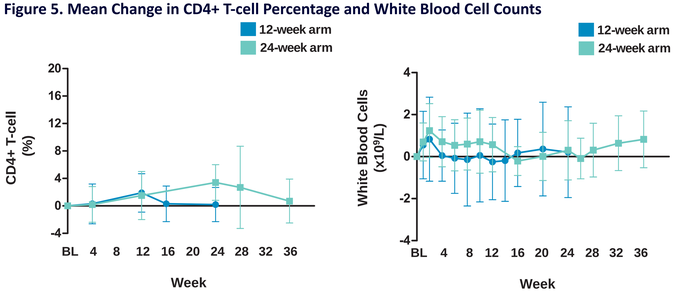
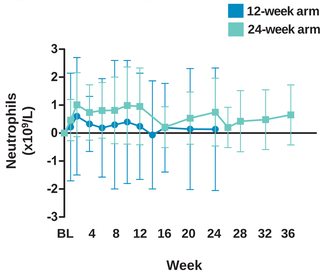


Figure 5. Mean Change in CD4+ T-cell Percentage and White Blood Cell Counts



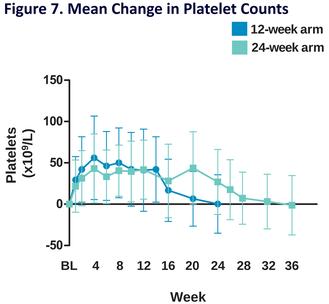
- In patients in the 12-week arm, mean change (SD) in neutrophil count was 0.24 (1.899) x10^9/L at treatment week 12. In patients in the 24-week arm, mean change (SD) in neutrophil count was 0.75 (1.213) x10^9/L at treatment week 24 **(Figure 6)**

Figure 6. Mean Change in Neutrophil Counts



- In patients in the 12-week arm, mean change (SD) in platelet count was 41.1 (49.70) x10^9/L at treatment week 12. In patients in the 24-week arm, mean change (SD) in platelet count was 26.9 (39.34) x10^9/L at treatment week 24 **(Figure 7)**. No patient had clinically significant abnormalities in platelet counts (counts <50 x10^9/L)

Figure 7. Mean Change in Platelet Counts



CONCLUSIONS

- Among HCV/HIV-1 co-infected treatment-naïve and -experienced patients, hemoglobin declines to <10 g/dL were infrequent with 3D + RBV treatment. All patients whose RBV dose was modified due to declines in hemoglobin achieved SVR12
- The observed rates of anemia may be due to the absence of IFN and its bone marrow suppressive effects on reticulocytosis
- Transient declines in absolute CD4+ T-cells paralleled changes in total lymphocyte count, which is consistent with known effects of RBV on the lymphocyte population, as seen in other trials of direct-acting antiviral treatment in co-infected patients[8–10]

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