UNITY-2: Daclatasvir/Asunaprevir/Beclabuvir ± RBV for HCV Genotype 1 With Cirrhosis

Poster 688

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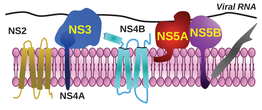
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BACKGROUND

- Chronic HCV infection is associated with progressive liver disease that can lead to cirrhosis and hepatocellular carcinoma
  - Globally, 130-150 million people are chronically infected, resulting in up to 350,000 deaths per year[1,2]
  - Cirrhosis can reduce response to HCV therapies – potent, well-tolerated all-oral regimens are required
- Direct-acting antiviral (DAA) regimens, even with ribavirin (RBV), can require more than 12 weeks of treatment to maximize sustained virologic response (SVR) rates in patients with cirrhosis[3,4]
- In phase 2 studies daclatasvir + asunaprevir + beclabuvir (BMS-791325) achieved SVR12 in > 92% (genotype [GT]1) or 100% (GT 4) of treatment-naive patients with 12 weeks of treatment[5,6]
- The phase 3 UNITY-2 study evaluated this regimen as a fixed-dose combination, with or without ribavirin, in treatment-naive or experienced patients with GT 1 infection and compensated cirrhosis

ALL-ORAL DCV-TRIO REGIMEN

- **Daclatasvir (DCV)**
  - Pangenotypic[a] NS5A inhibitor, low potential for drug–drug interactions
  - Safe and well tolerated
  - Studied in > 13,000 patients
  - Approved in Europe and Japan; under regulatory review in the US
- **Asunaprevir (ASV)**
  - NS3 protease inhibitor
  - Clinical data in GT 1 and 4
- **Beclabuvir (BCV)**
  - Non-nucleoside NS5B polymerase inhibitor
  - Clinical data in GT 1 and 4

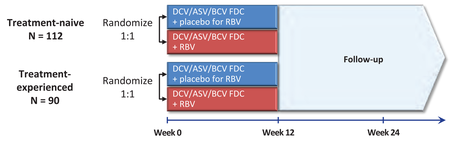


- **DCV / ASV / BCV co-formulated as twice-daily fixed-dose combination**

[a] Pangenotypic: GT 1-6 *in vitro* and GT 1-4 in clinical trials

METHODS

Figure 1. UNITY-2 Study Design (AI443-113)



Treatment Regimen

- Twice-daily fixed-dose combination (FDC)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg
  - With or without weight-based ribavirin twice-daily

METHODS (cont)

Primary Endpoint

- SVR12 in treatment-naive patients with cirrhosis
  - HCV RNA < LLOQ (25 IU/mL) target detected (TD) or target not detected (TND) at posttreatment Week 12
  - Demonstrate SVR12 is significantly greater than historical threshold of 69%

Key Secondary Endpoints

- SVR12 in treatment-experienced patients with cirrhosis
  - HCV RNA < LLOQ (25 IU/mL) TD or TND at posttreatment Week 12
  - Demonstrate SVR12 is significantly greater than historical threshold of 45%
- Safety, as measured by frequencies of discontinuations due to adverse events (AEs) and serious AEs

Inclusion Criteria

- Adults with HCV GT 1a or 1b infection, ≥ 18 years of age
- Compensated Child-Pugh class A cirrhosis, confirmed by
  - Liver biopsy (METAVIR F4), or
  - Fibroscan > 14.6 kPa, or
  - FibroTest ≥ 0.75 with APRI (AST/platelet ratio index) > 2
- Platelets > 50,000/mm^3; INR < 1.7; albumin > 3.5 g/dL

Two Cohorts

- Treatment-naive: with no previous exposure to an interferon formulation (i.e., IFN, pegIFN), RBV, or HCV DAA
- Treatment-experienced: prior exposure to peginterferon/ribavirin and/or select DAAs[a] or host-targeted agents

[a] DAAs excluded: prior exposure to NS5B non-nucleoside thumb-1 inhibitors, NS3 inhibitors or NS5A inhibitors.

RESULTS

Table 1. Demographic and Baseline Disease Characteristics

Parameter	Treatment-naive DCV-TRIO N = 57	Treatment-naive DCV-TRIO+RBV N = 55	Treatment-experienced DCV-TRIO N = 45	Treatment-experienced DCV-TRIO+RBV N = 45
Age, median years (range)	58 (25-75)	59 (35-73)	59 (19-76)	60 (48-73)
Male, n (%)	39 (68)	35 (64)	32 (71)	27 (60)
Race, n (%)				
White	49 (86)	51 (93)	41 (91)	37 (82)
Black/African American	6 (11)	6 (11)	2 (4)	6 (13)
Other	2 (4)	3 (5)	2 (4)	2 (4)
HCV RNA ≥ 800K IU/mL, n (%)	47 (82)	41 (75)	43 (96)	41 (91)
HCV GT subtype[a] n (%)				
1a	40 (70)	39 (71)	35 (78)	35 (78)
1b	17 (30)	15 (27)	10 (22)	10 (22)
6	0 (0)	1 (2)	0	0
IL28B genotype, n (%),				
CC	13 (23)	18 (33)	15 (33)	9 (20)
CT	30 (53)	35 (64)	20 (44)	27 (60)
TT	13 (23)	2 (4)	10 (22)	9 (20)
Not reported	1 (2)	0	0	0
Prior treatment outcome				
Posttreatment relapse	-	-	8 (18)	8 (18)
Null response[b]	-	-	19 (42)	16 (36)
Partial response	-	-	6 (13)	2 (4)
Other	-	-	12 (27)	19 (42)

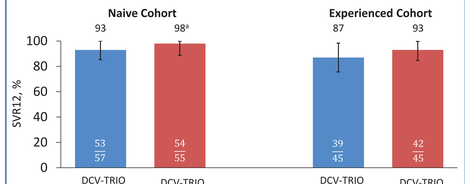
[a]One patient in treatment-naïve DCV- TRIO + RBV group had GT 6 infection.
[b] Null response defined as <2 $\log_{10}$ decrease in HCV RNA at treatment Week 12 compared with baseline

Patients

- Most patients were GT 1a-infected (74%), male (66%) and white (86%)
- Cirrhosis was confirmed by liver biopsy (n = 108), Fibroscan (n = 79), or FibroTest/APRI (n = 15)
- Platelet counts were < 100,000/mm^3 in 53 patients (26%)
- Overall, 99% of patients competed the treatment period, including all (100%) treatment-naive patients and 97% of experienced patients

RESULTS (cont)

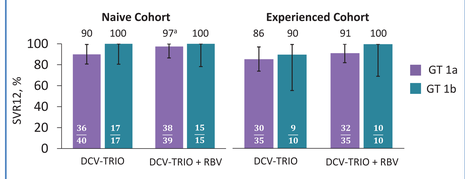
Figure 2: Virologic Response : SVR12 (mITT)



[a] One patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.
Error bars indicate 97.5% confidence intervals.

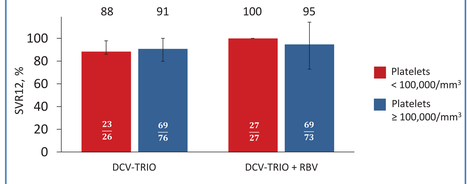
- The SVR12 rate in treatment-naive patients (93%, 98%) was significantly higher than the historical threshold rate (69%)
  - The lower bound confidence interval (97.5%) exceeded the threshold value
- The SVR12 rate in treatment-experienced patients (87%, 93%) was significantly higher than the historical threshold rate (45%)
  - The lower bound confidence interval (97.5%) exceeded the threshold value

Figure 3: Virologic Response - SVR12 by GT 1 Subtype



[a]One patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.
Error bars indicate 95% confidence intervals.

Figure 4: SVR12 by Baseline Platelets



- Responses were also comparable by gender, age, baseline HCV RNA, and *IL28B* genotype

RESULTS (cont)

Table 2: Virologic Outcomes

Outcome, n (%)	Treatment-naive DCV-TRIO N = 57	Treatment-naive DCV-TRIO + RBV N = 55	Treatment-experienced DCV-TRIO N = 45	Treatment-experienced DCV-TRIO + RBV N = 45
SVR12	53 (93)	54 (98)	39 (87)	42 (93)
On-treatment failures				
Virologic breakthrough	0	0	1 (2)	1 (2)
Detectable HCV RNA at EOT	0	0	0	1 (2)
Posttreatment failures				
Relapse	4 (7)	0	5 (11)	1 (2)
Missing data[a]	0	1 (2)	0	0

[a] 1 treatment-naive patient on DCV-TRIO + RBV was < LLOD TND at EOT and follow-up Week 4 but no HCV RNA at follow-up Week 8 and subsequent visits.

Resistance Analyses

Resistance-associated variants (RAVs) at baseline[a]

- NS5A (28, 30, 31, 93) and NS3 (168) RAVs did not appear to impact SVR12
  - 26/28 patients with NS5A RAVs achieved SVR12
  - 2/2 patients with NS3 RAVs achieved SVR12
- NS5B-P495 variants not detected at baseline

Table 3: Emergent RAVs in Virologic Failures[a]

Patient	GT	Outcome	NS5A	NS3	NS5B
1	1a	On-treatment failure	Q30R/H	None	None
2	1a	On-treatment failure	Q30E	R155K	P495P/L
3	1a	On-treatment failure	Q30E	R155K	P495S
4	1a	Relapse	None	None	None
5	1a	Relapse	Q30H	R155K	None
6	1a	Relapse	Y93N	R155K	None
7	1a	Relapse	Q30R, L31M/I	R155K/R, D168D/E	A421V
8	1a	Relapse	L31V	R155K	None
9	1a	Relapse	Q30R, L31M/L	R155K	None
10	1a	Relapse	M28G	R155K	None
11	1a	Relapse	Q30H, L31V	R155K	None
12	1a	Relapse	Y93N	R155K	None
13	1b	Relapse	Y93H	None	None

[a] Population-based sequencing

Table 4: On-Treatment Safety and Tolerability

Event, n (%)	DCV-TRIO N = 102	DCV-TRIO + RBV N = 100
Serious AEs[a]	2 (2)	7 (7)
Discontinued RBV due to AE[b]	0	3 (3)
AE leading to discontinuation[c]	0	1 (1)
AEs (any grade) in ≥ 10% of patients		
Fatigue	12 (12)	28 (28)
Headache	17 (17)	23 (23)
Nausea	14 (14)	17 (17)
Diarrhea	13 (13)	9 (9)
Insomnia	6 (6)	15 (15)
Pruritus	6 (6)	15 (15)
Grade 3/4 Lab Abnormalities		
Hemoglobin < 9.0 g/dL	0	5 (5)
Platelets < 50 × 10^9 /L	2 (2)	2 (2)
Leukocytes < 1.5 × 10^9 /L	0	1 (1)
Lymphocytes < 0.5 × 10^9 /L	1 (1)	3 (3)
Neutrophils < 0.75 × 10^9 /L	1 (1)	1 (1)
ALT > 5.0 x ULN	3 (3)	1 (1)
AST > 5.0 x ULN	2 (2)	1 (1)
Total bilirubin > 2.5 x ULN	0	3 (3)
Total lipase > 3.0 x ULN	5 (5)	1 (1)

[a] Three SAEs considered treatment-related: anemia, ALT and total bilirubin elevations, RBV overdose.
[b] Three patients discontinued RBV due to anemia or cough; all achieved SVR12.
[c] Discontinued all study medication (due to anemia followed by ALT and total bilirubin elevations); achieved SVR12.

RESULTS (cont)

- Both DCV TRIO and DCV-TRIO + RBV therapies were generally safe and well tolerated, with low rates of serious AEs and AEs leading to discontinuations
- One patient had concurrent ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN at Week 6 and discontinued treatment. Lab abnormalities resolved after discontinuation of study drugs; achieved SVR12
- The most commonly observed AEs were fatigue, headache, nausea, and diarrhea
- Higher AE rates were observed in patients exposed to regimen with RBV

SUMMARY

- Treatment with the DCV/ASV/BCV fixed-dose combination (DCV-TRIO), with or without RBV, in patients with GT 1 and compensated cirrhosis achieved high SVR12 rates after 12 weeks of treatment
  - 98% in naive, 93% in experienced patients with DCV-TRIO + RBV
  - 93% in naive, 87% in experienced patients with DCV-TRIO alone
- SVR12 rates were comparable with respect to gender, age, race, baseline HCV RNA, and *IL28B* genotype
  - No apparent impact of thrombocytopenia on SVR12
- Addition of RBV decreased relapse frequency in GT 1a
- Baseline RAVS do not appear to impact response
- DCV-TRIO ± RBV was generally safe and well tolerated

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