All-Oral, Fixed-Dose Combination Therapy With Daclatasvir/Asunaprevir/Beclabuvir for Non-Cirrhotic Patients With Chronic HCV Genotype 1 Infection: UNITY-1 Phase 3 SVR12 Results

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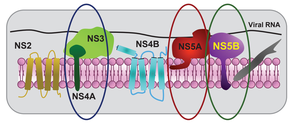
Poster LB-7

BACKGROUND

- Globally, 130–150 million people are chronically infected with HCV, resulting in up to 350,000 deaths per year[1,2]
  - Chronic HCV infection is associated with progressive liver disease that can lead to cirrhosis and hepatocellular carcinoma
- The all-oral combination of daclatasvir, asunaprevir, and beclabuvir achieved sustained virologic response (SVR12) rates of > 92% in genotype (GT) 1 treatment-naive patients and 100% in GT 4 patients with 12 weeks of treatment in Phase 2 studies[3,4]
- Here we present results of the Phase 3 UNITY-1 study evaluating this all-oral, ribavirin-free combination in non-cirrhotic treatment-naive and -experienced patients with HCV GT 1 infection
- Safety and efficacy in GT 1 cirrhotic patients are reported at this congress (Late-Breaker Oral LB-2)

ALL-ORAL DCV-TRIO REGIMEN

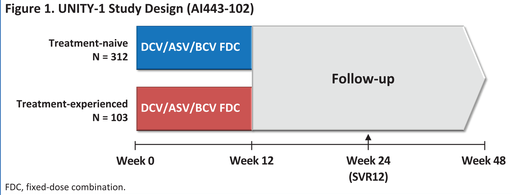
- **Daclatasvir (DCV)**
  - Pangenotypic[a] NS5A inhibitor with low potential for drug–drug interactions
  - Safe and well tolerated in > 6000 subjects
  - Approved in Europe and Japan; under regulatory review in the US
- **Asunaprevir (ASV)**
  - NS3 protease inhibitor
  - Clinical data in GT 1 and 4
- **Beclabuvir (BCV; BMS-791325)**
  - Non-nucleoside NS5B polymerase inhibitor
  - Clinical data in GT 1 and 4
- **DCV/ASV/BCV co-formulated as a twice-daily, fixed-dose combination**



[a] Pangenotypic: GT 1–6 in vitro and GT 1–4 in clinical trials.

METHODS

Figure 1. UNITY-1 Study Design (AI443-102)



FDC, fixed-dose combination.

Primary Endpoint

- SVR12 in treatment-naive patients
  - HCV RNA < lower limit of quantitation (LLOQ) at posttreatment Week 12
  - Demonstrate SVR12 is significantly greater than historical threshold of 79% (based on an analysis of sofosbuvir plus peginterferon/ribavirin data)
  - Assessed using the Roche HCV COBAS TaqMan® test v2.0 (LLOQ, 25 IU/mL)

Treatment Regimen

- Twice-daily, fixed-dose combination tablet (DCV-TRIO)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg

Key Secondary Endpoints

- SVR12 in treatment-experienced patients
  - Demonstrate SVR12 is significantly greater than historical threshold of 48% (based on an analysis of simeprevir plus peginterferon/ribavirin data)
- Safety: assessed by the frequency of serious adverse events (AEs) and discontinuations due to AEs

Patients

- Non-cirrhotic patients with chronic HCV GT 1 infection
- Aged ≥ 18 years with HCV RNA ≥ 10,000 IU/mL
- No evidence of HIV or hepatitis B virus coinfection or hepatic decompensation
- *Treatment-naive:* no prior exposure to interferon alfa, ribavirin or any direct-acting antiviral (DAA) or host-targeted agent
- *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

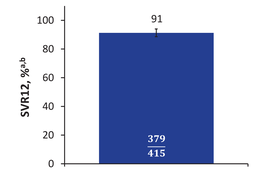
Table 1. Baseline Demographic and Disease Characteristics

Parameter	Treatment-naive N = 312	Treatment-experienced N = 103	Total N = 415
Age, median years (range)	53.5 (19–77)	57.0 (22–69)	55.0 (19–77)
Male, n (%)	175 (56)	64 (62)	239 (58)
Race, n (%)			
White	270 (87)	91 (88)	361 (87)
Black/African American	34 (11)	7 (7)	41 (10)
Other	8 (3)	5 (5)	13 (3)
HCV RNA, n (%)			
< 800,000 IU/mL	68 (22)	10 (10)	78 (19)
≥ 800,000 IU/mL	244 (78)	93 (90)	337 (81)
HCV GT 1 subtype, n (%)			
1a	229 (73)	75 (73)	304 (73)
1b	83 (27)	28 (27)	111 (27)
IL28B genotype (rs 12979860), n (%)			
CC	90 (29)	16 (16)	106 (26)
CT	174 (56)	73 (71)	247 (60)
TT	47 (15)	14 (14)	61 (15)
Not reported	1 (0.3)	0	1 (0.2)
Prior IFN-based treatment, n (%)	N/A	93 (90)	93 (22)
Prior treatment outcome			
Posttreatment relapse	–	39 (38)	39 (9)
Null response[a]	–	25 (24)	25 (6)
Partial response	–	12 (12)	12 (3)
Interferon intolerant	–	7 (7)	7 (2)
Indeterminate[b]	–	10 (10)	10 (2)
Other prior anti-HCV treatment, n (%)	N/A	10 (10)	10 (2)

[a] Null response defined as <2 $\log_{10}$ decrease in HCV RNA at treatment Week 12 compared with baseline.
[b] Prior treatment response missing or could not be categorized.

- The majority of patients (73%) were infected with HCV GT 1a
- Most were male (58%) and white (87%), and the median age was 55 years
- Both treatment-naive and -experienced patients were predominately non-CC *IL28B* genotype (71% and 84%, respectively)
- The majority of patients (97%) completed the treatment period
  - 8 patients (6 naive, 2 experienced) discontinued due to lack of efficacy
  - 3 patients discontinued due to an AE; all achieved SVR12
  - 1 patient discontinued due to pregnancy at Week 6 and achieved SVR12

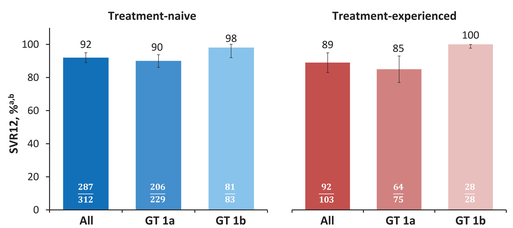
Figure 1. Overall SVR12 Rates



[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

- Overall, SVR12 was achieved by 91% of HCV genotype 1-infected patients

Figure 2. SVR12 Rates by Patient Population



[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

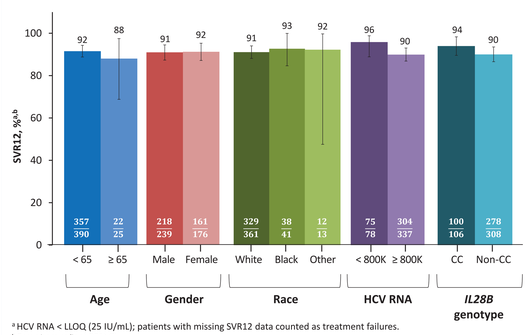
- The SVR12 rate in treatment-naive HCV GT 1 patients (92%) was significantly higher than the historical threshold rate (79%)
  - The lower bound 95% confidence interval (89%) exceeded the threshold value
- A significantly higher SVR12 rate was observed in treatment-experienced HCV GT 1 patients (89%) compared with the historical threshold rate (48%)
- High SVR12 rates (98–100%) were observed in treatment-naive and treatment-experienced patients infected with HCV GT 1b

RESULTS (cont)

Table 2. Other Virologic Endpoints

Parameter, n (%)	Treatment-naive N = 312	Treatment-experienced N = 103
HCV RNA undetectable at:		
Week 4	248 (79)	71 (69)
End of treatment	301 (96)	98 (95)
HCV RNA <LLOQ at posttreatment:		
Week 4 (SVR4)	292 (94)	92 (89)
Week 8 (SVR8)	284 (91)	91 (88)
Week 12 (SVR12)	287 (92)	92 (89)

Figure 3. SVR12 by Baseline Factors



[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

- SVR12 rates were high across patient subgroups based on baseline characteristics

Table 3. Virologic Outcomes

Outcome, n (%)	Treatment-naive N = 312	Treatment-experienced N = 103
SVR12	287 (92)	92 (89)
On-treatment failures		
Virologic breakthrough	6 (2)	2 (2)
Detectable HCV RNA at EOT	3 (1)	2 (2)
Posttreatment failures[a]		
Relapse	15 (5)	6 (6)
Missing HCV RNA	1 (0.3)	1 (1)

[a] Percentages based on number of patients with undetectable HCV RNA at end of treatment (EOT) (treatment-naive: n = 301; treatment-experienced: n = 98).

- Baseline NS5A resistance-associated variants were detected in 34/302 GT 1a patients[b] and 17/106 GT 1b patients with available data
  - 25/34 GT 1a patients achieved SVR12
  - All 17 GT 1b patients achieved SVR12
- Virologic failure occurred in 34/415 patients
  - NS5A-Q30, NS3-R155 and NS5B-P495 were the most frequently observed resistance-associated variants among GT 1a patients[b]
  - Only 2 GT 1b patients experienced virologic failure
    - 1 patient had GT 2b sequence at virologic failure and 1 had a non-GT 1a/1b at subsequent analysis[c]

[b] Resistance was performed by population-based sequencing on samples with HCV RNA ≥1000 IU/mL.
[c] Patients were classified as GT 1b by the commercial Abbott HCV Genotype II or VERSANT® HCV genotype 2.0 LiPA assay.

RESULTS (cont)

Table 5. On-Treatment Safety Summary

Parameter, n (%)	All patients N = 415
Death[a]	1 (0.2)
Serious AEs[b]	7 (2)
AEs leading to discontinuation[c]	3 (0.7)
Any AE	328 (79)
Most frequent AEs (≥ 10% of patients)	
Headache	107 (26)
Fatigue	69 (17)
Diarrhea	58 (14)
Nausea	56 (13)
Grade 3/4 laboratory abnormalities	
Hemoglobin < 9.0 g/dL	0
Absolute neutrophils < 0.75 × 10^9 /L	2 (0.5)
Absolute lymphocytes < 0.5 × 10^9 /L	1 (0.2)
Platelets < 50 × 10^9 /L	0
Alanine aminotransferase > 5 × ULN	19 (5)
Aspartate aminotransferase > 5 × ULN	9 (2)
Total bilirubin > 2.5 × ULN	0
Total lipase > 3.0 × ULN	16 (4)

AE, adverse event; ULN, upper limit of normal.
[a] 1 death was reported at posttreatment Week 3 due to a heroin overdose and was not considered related to treatment.
[b] All serious AEs were not considered related to study medication.
[c] Patients discontinued due to a treatment-related AE (insomnia, ALT elevation, ALT/AST elevation); all achieved SVR12.

- DCV-TRIO was well tolerated with low rates of serious AEs (2%) and AE discontinuations (0.7%)
- The most commonly observed AEs were headache, fatigue, diarrhea, and nausea
- Treatment discontinuation due to an ALT elevation occurred in 2 patients:
  - A 43-year-old male whose ALT rose to a maximum of 579 U/L on Day 43; total bilirubin (T_{BILI}) peak was 0.9 mg/dL; treatment was discontinued on Day 46 and the ALT elevation resolved at Day 81
  - A 58-year-old male with elevated ALT on Day 56 (188 U/L) and Day 77 (833 U/L). T_{BILI} reached 2.3 mg/dL. Treatment was stopped on Day 78; on Day 79, ALT reached maximum of 862 U/L (T_{BILI} was 1.6 mg/dL); both resolved on Day 98
- 1 death occurred at posttreatment Week 3 due to a heroin overdose and was not considered to be related to study medication by the investigator

SUMMARY

- Treatment with the all-oral, ribavirin-free, fixed-dose combination of DCV/ASV/BCV (DCV-TRIO) for 12 weeks achieved an SVR12 of 91% in non-cirrhotic GT 1 patients
- SVR12 rates were comparable with respect to gender, age, race, baseline HCV RNA, and *IL28B* genotype
- DCV-TRIO was generally safe and well tolerated
  - Low rates of serious AEs and AEs leading to discontinuation

The safety and efficacy results of DCV-TRIO in treatment-naive and -experienced GT 1-infected patients with cirrhosis (UNITY-2) will be presented at this meeting (Muir A, et al. Late-Breaker Oral LB-2)

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