UNITY-1: Daclatasvir/Asunaprevir/Beclabuvir for HCV Genotype 1 Without Cirrhosis

Poster 687

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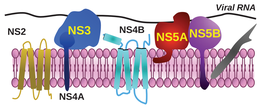
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BACKGROUND

- Globally, 130–150 million people are chronically infected with HCV, resulting in up to 350,000 deaths per year[1,2]
- 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 treatment-naive and -experienced patients without cirrhosis infected with HCV GT 1

ALL-ORAL DCV-TRIO REGIMEN

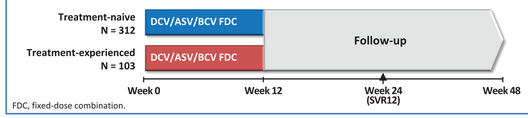
- Daclatasvir (DCV)
  - Pangenotypic[a] NS5A inhibitor, low potential for drug–drug interactions
  - Safe and well tolerated
  - Studied in > 13,000 patients
  - Approved in Europe and Japan; under regulatory review in the US
- Asunaprevir (ASV)
  - NS3 protease inhibitor
  - Clinical data in GT 1 and 4
- Beclabuvir (BCV; 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[a]
  - 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 (lower limit of quantitation [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 any interferon formulation, ribavirin or any direct-acting antiviral (DAA) or host-targeted agent
- *Treatment-experienced:* prior exposure to peginterferon/ribavirin and/or select DAAs[b] or host-targeted agents

[a] HCV RNA < LLOQ at posttreatment Week 12
[b] DAAs excluded: prior exposure to NS5B non-nucleoside thumb-1 inhibitors, NS3 inhibitors or NS5A inhibitors.

RESULTS

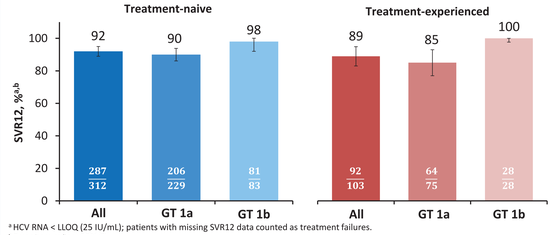
Table 1. Baseline Demographic and Disease Characteristics

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.

- Median age was 55 years; the majority of patients were male (58%) and white (87%)
- Most patients (73%) were infected with HCV GT 1a
- Patients in the treatment-naive and -experienced cohorts 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 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.

- Overall, 91% of HCV genotype 1-infected patients achieved SVR12
- A significantly higher SVR12 rate was observed in treatment-naive HCV GT 1 patients (92%) compared with the historical threshold rate (79%)
  - The lower bound 95% confidence interval (89%) exceeded the threshold value
- The SVR12 rate in treatment-experienced HCV GT 1 patients (89%) was significantly higher than 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)

- SVR12 rates were high across patient subgroups based on gender age, race, baseline HCV RNA and *IL28B* genotype

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)
Other posttreatment non-response	1 (< 1)[b]	1 (< 1)[c]

[a] Rates based on patients with undetectable HCV RNA at end of treatment (EOT): treatment-naive, n = 301; treatment-experienced, n = 98.
[b] Patient was lost to follow-up after posttreatment Week 4; [c] Patient died before posttreatment Week 4.

- Virologic failure occurred in 34/415 patients
- Analysis of resistance-associated variants (RAVs) at failure in GT 1a patients:[b]
  - 28/29 patients had NS5A RAVs; NS5A-Q30 RAV was observed most frequently (18 patients)
  - 25/26 patients had NS3 RAVs; NS3-R155 was observed most frequently (22 patients)
  - 12/28 patients had NS5B RAVs; NS5B-P495 was observed most frequently (11 patients)
  - 25 patients had all three viral sequences (NS5A, NS3, NS5B) available at virologic failure
    - 10 patients had RAVs to all 3 drugs (5 viral breakthrough, 4 detectable HCV RNA at EOT, 1 relapse)
    - 14 patients had only NS5A and NS3 RAVs (1 viral breakthrough, 1 detectable HCV RNA at EOT, 12 relapse)
- Only 2 GT 1b-infected 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 testing was performed in patients by population-based sequencing on samples with HCV RNA ≥1000 IU/mL; analysis includes patients with available baseline and failure sequences.
[c] Patients were classified as GT 1b by the commercial Abbott HCV Genotype II or VERSANT® HCV genotype 2.0 LiPA assay.

Table 4. SVR12 rates by baseline NS5A RAVs

n/N (%)[a]	NS5A RAV	Treatment-naive N = 312	Treatment-experienced N = 103	Total N= 415
GT 1a	M28: L/I/T/V	12/17 (71)	8/9 (89)	20/26 (77)
	Q30: H/R	0/5 (0)	1/1 (100)	1/6 (17)
	L31: M	2/2 (100)	2/2 (100)	4/4 (100)
	Y93: C/H	1/2 (50)	0	1/2 (50)
GT 1b	L28M/V	1/1 (100)	1/1 (100)	2/2 (100)
	R30: Q	3/3 (100)	1/1 (100)	4/4 (100)
	L31: I/M	3/3 (100)	1/1 (100)	4/4 (100)
	Y93: H	6/6 (100)	3/3 (100)	9/9 (100)

[a] Number of patients achieving SVR12 / number of patients with baseline polymorphism (%).

- Baseline NS5A resistance-associated variants were detected in 34/302 GT 1a patients and 17/106 GT 1b patients with available data
  - 25/34 GT 1a patients achieved SVR12
    - 4/9 not achieving SVR12 had baseline RAVS conferring ≥1000-fold reduction in susceptibility to DCV (Q30H [2 patients], M28T-Q30R, and Q30H-Y93H)
  - All 17 GT 1b patients achieved SVR12
- No association between baseline NS3 or NS5B RAVs and SVR12 was observed

RESULTS (cont)

Table 5. On-Treatment Safety Summary

Parameter, n (%)	All patients (N = 415)
Death[a]	1 (0.2)
Serious AEs[b]	7 (1.7)
AEs leading to discontinuation[c]	3 (0.7)
Most frequent AEs (≥ 10% of patients)	
Headache	107 (25.8)
Fatigue	69 (16.6)
Diarrhea	58 (14.0)
Nausea	56 (13.5)
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 (4.6)
Aspartate aminotransferase > 5 × ULN	9 (2.2)
Total bilirubin > 2.5 × ULN	0
Total lipase > 3.0 × ULN	16 (3.9)

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%)
- AEs of headache, fatigue, diarrhea, and nausea were observed most frequently (**Table 5**)
- 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 by gender, age, race, baseline HCV RNA, and *IL28B* genotype
- Among patients with NS5A RAVs at baseline, SVR12 was achieved by all (17/17) GT 1b patients and 25/34 GT 1a-infected patients
- DCV-TRIO was generally safe and well tolerated

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