High Rate of Sustained Virologic Response With the All-Oral Combination of Daclatasvir (NS5A Inhibitor) Plus Sofosbuvir (Nucleotide NS5B Inhibitor), With or Without Ribavirin, in Treatment-Naive Patients Chronically Infected With HCV GT 1, 2, or 3

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Eley T, Wind-Rotolo M, Huang S-P, Gao M, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, and Grasela DM for the AI444040 Study Group

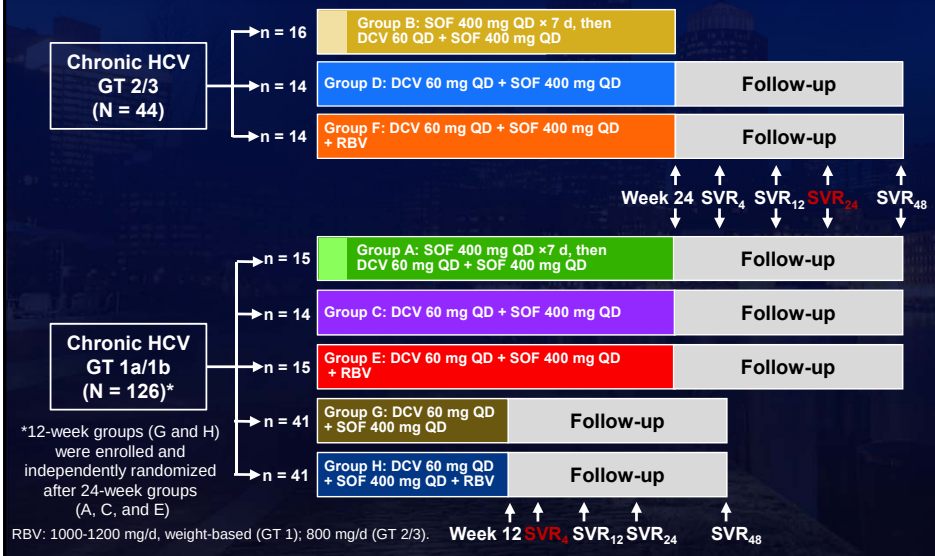
Abstract LB-2

Background

- Oral combinations of direct-acting antivirals, without peginterferon alfa, may provide new options for patients with chronic HCV infection
- Daclatasvir (DCV; BMS-790052) is a first-in-class NS5A replication complex inhibitor[1,2]
- Sofosbuvir (SOF; GS-7977) is a nucleotide analogue NS5B polymerase inhibitor[3,4]
- Both DCV and SOF have potent antiviral activity, broad genotypic coverage *in vitro*, and once-daily oral administration[1-5]
- Both have achieved high sustained virologic response (SVR) rates in previously untreated HCV genotype (GT) 1–infected patients when combined with peginterferon alfa and ribavirin (RBV)[5-6]

1. Gao M, et al. Nature 2010; 465:96-100; 2. Nettles RE, et al. Hepatology 2011; 54:1956-1965; 3. Sofia MJ, et al. J Med Chem 2010; 53:7202-7218; 4. Lam AM, et al. Antimicrob Agents Chemother 2012; 56:3359-3368; 5. Kowdley KV, et al. J Hepatol 2012; 56(Suppl2):S1; 6. Pol S, et al. Lancet Infect Dis 2012; 12:671-677.

Randomized, Open-label, 2-Stage, Parallel-Group Phase 2a Study: AI444-040



*12-week groups (G and H) were enrolled and independently randomized after 24-week groups (A, C, and E)

RBV: 1000-1200 mg/d, weight-based (GT 1); 800 mg/d (GT 2/3).

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Baseline Demographics and Disease Characteristics

Parameter	Genotype 2/3			Genotype 1				
	B SOF LI + DCV (N = 16)	D DCV + SOF (N = 14)	F DCV + SOF + RBV (N = 14)	A SOF LI + DCV (N = 15)	C DCV + SOF (N = 14)	E DCV + SOF + RBV (N = 15)	G DCV + SOF (N = 41)	H DCV + SOF + RBV (N = 41)
Age, median years	51	50	52	56	54	54	55	54
Male gender, n (%)	11 (69)	6 (43)	5 (36)	7 (47)	9 (64)	7 (47)	20 (49)	21 (51)
Race,[a] n (%)								
White	16 (100)	10 (71)	12 (86)	11 (73)	11 (79)	12 (80)	33 (81)	33 (81)
Black/AA	0	2 (14)	0	4 (27)	3 (21)	2 (13)	5 (12)	7 (17)
HCV RNA, mean log_{10} IU/mL (SD)	6.5 (0.7)	6.8 (0.5)	6.6 (0.6)	6.5 (0.5)	6.6 (0.3)	6.7 (0.6)	6.2 (0.5)	6.4 (0.6)
HCV genotype, n (%)								
1a	0	0	0	11 (73)	10 (71)	11 (73)	33 (81)	33 (81)
1b	0	0	0	4 (27)	4 (29)	4 (27)	8 (20)	8 (20)
2	9 (56)	8 (57)	9 (64)	0	0	0	0	0
3	7 (44)	6 (43)	5 (36)	0	0	0	0	0
IL28B genotype (rs12979860), n (%)								
CC	8 (50)	5 (36)	7 (50)	4 (27)	8 (57)	4 (27)	9 (22)	15 (37)
METAVIR score[b] n (%)								
F0 – F1	6 (38)	6 (43)	6 (43)	4 (27)	6 (43)	6 (40)	15 (37)	13 (32)
F2 – F3	7 (44)	7 (50)	6 (43)	8 (53)	7 (50)	6 (40)	19 (46)	22 (54)
> F3	3 (19)	1 (7)	2 (14)	3 (20)	1 (7)	2 (13)	6 (15)	5 (12)

[a] Other: E, n = 1; G, n = 3; H, n = 1; D, n = 2; F, n = 2; [b] Derived from FibroTest result: conversion based on table on FibroTest manufacturer's website, score missing: E, n = 1; G, n = 1; H, n = 1

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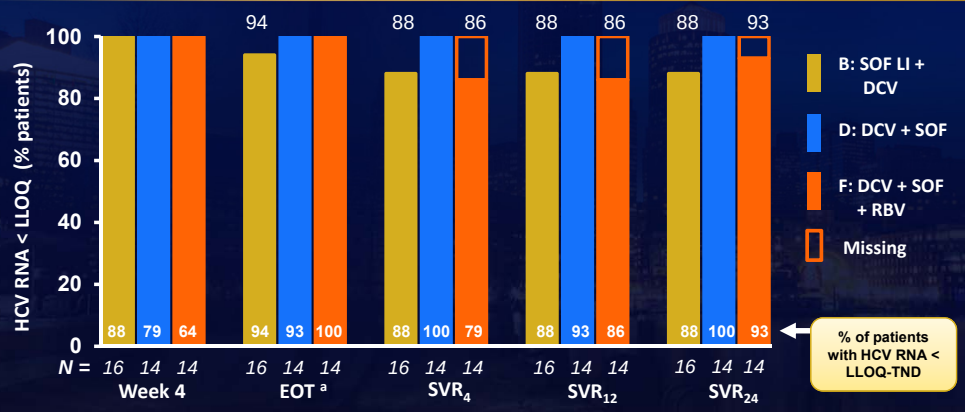
Genotype 2/3: Virologic Response During and After Treatment (mITT)



Group B: 1 patient (GT3) relapsed; NS5A-A30K polymorphism (associated with DCV resistance) detected at baseline and PT Week 4. 1 patient (GT3) met protocol definition of virologic breakthrough; added pegIFN alfa/RBV – achieved SVR_{24}

Group F: 2 lost to follow-up after EOT; 1 returned at PT Week 24 with HCV RNA < LLOQ-TND

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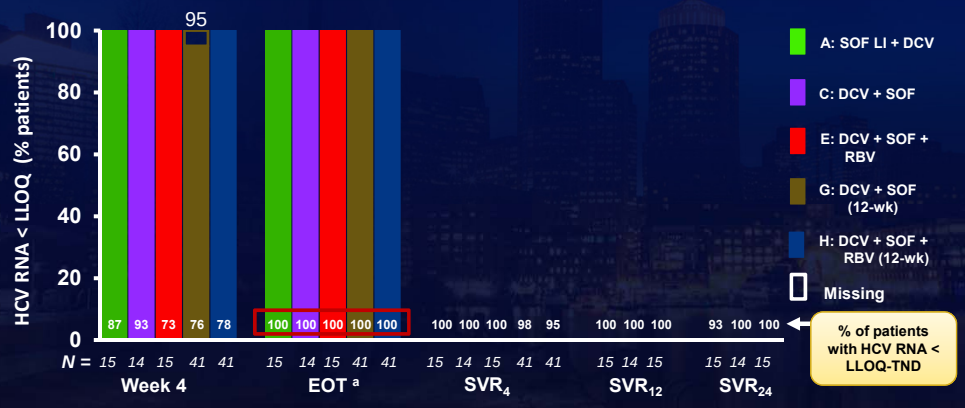
Genotype 1: Virologic Response During and After Treatment, 12- and 24-Week Groups (mITT)



[a] End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT.

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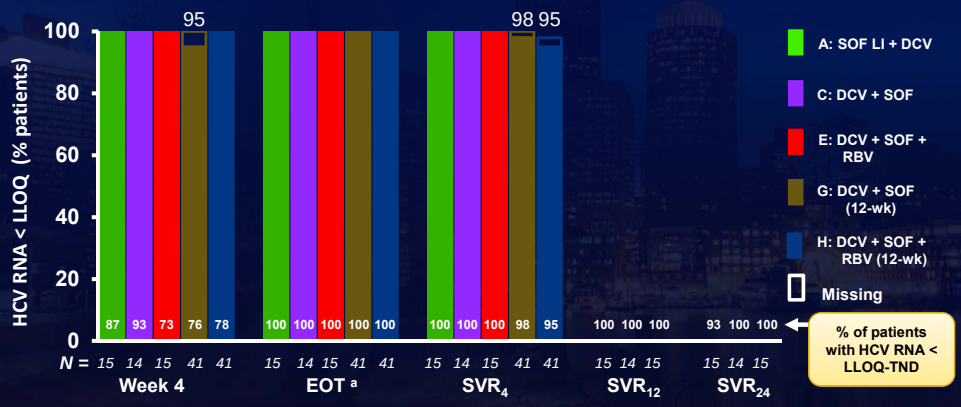
Genotype 1: Virologic Response During and After Treatment, 12- and 24-Week Groups (mITT)



12-week Groups (G and H)

- 2 patients missing at PT Week 4— both achieved SVR_{12}; 1 patient undetectable at PT Week 2 and with HCV RNA detected at PT Week 4 (not confirmed)—achieved SVR_{12}
- 68 patients have reached PT Week 12—all 68 have achieved SVR_{12}

[a] End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT.

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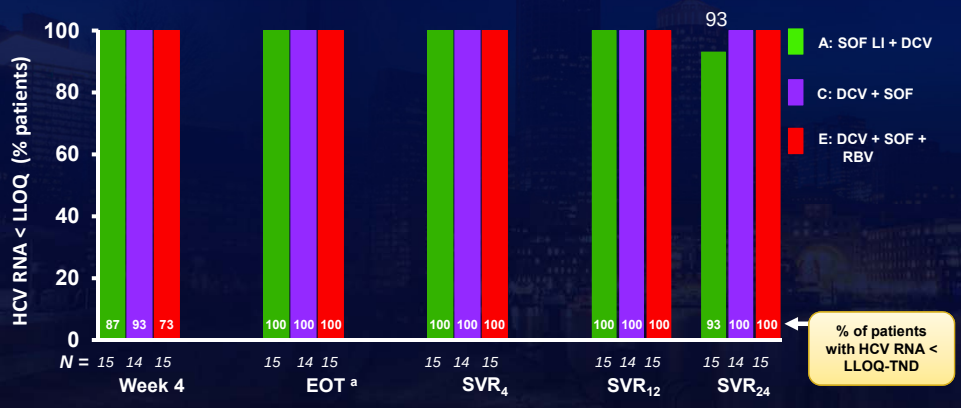
Genotype 1: Virologic Response During and After Treatment, 24-Week Groups (mITT)



- **Group A**: 1 patient with history of IDU became viremic at PT Week 24: posttreatment viral sequence clearly different from pretreatment virus, consistent with reinfection

[a] End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT.

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Safety On-Treatment

Patients with event, n (%)		24-week treatment			12-week treatment	
		A and B SOF LI + DCV (N = 31)	C and D DCV + SOF (N = 28)	E and F DCV + SOF + RBV (N = 29)	G DCV + SOF (N = 41)	H DCV + SOF + RBV (N = 41)
Safety parameters	Grade 3–4 AEs	0	4 (14)	2 (7)	1 (2)	1 (2)
	Discontinuations due to AEs	0	1 (4)	1 (3)	0	0
	SAEs[a]	2 (6)	4 (14)	2 (7)	1 (2)	0
	Hgb < 9 g/dL (grade 3–4)	0	0	6 (21)	0	5 (12)
Adverse events occurring in ≥ 20% of patients total	Fatigue	9 (29)	14 (50)	9 (31)	16 (39)	13 (32)
	Headache	5 (16)	8 (29)	11 (38)	14 (34)	9 (22)
	Nausea	5 (16)	9 (32)	9 (31)	8 (20)	8 (20)

- **Mean change in hemoglobin for RBV- vs non-RBV–containing regimens was -2.50 g/dL vs -0.65 g/dL after 12 weeks (Groups E, F, H vs A-D, G); and -1.98 g/dL vs -0.24 g/dL after 24 weeks (Groups E, F vs A–D)**
- **No grade 3–4 elevations of ALT, AST, or total bilirubin**

[a] Four events of overdose (extra study medication doses), classified as SAEs, are not included in the table: C and D, n = 1; E and F, n = 2; H, n = 1.

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Conclusions

- DCV + SOF with or without RBV achieved SVR in more than 93% of patients with HCV genotype 1, 2 or 3
- HCV genotype 1 (N = 126)
  - 12-week duration: SVR4 = 96%; all patients who have reached PT Week 12 (n = 68) have achieved SVR12 including the three patients not classified as SVR4
  - 24-week duration: SVR24 = 98%; one patient with re-infection posttreatment
- HCV genotype 2 or 3 (N = 44)
  - 24-week duration: SVR24 = 93% of patients; one patient with confirmed relapse (GT 3)
- Virologic response did not vary according to IL28B genotype, viral subtype, or the administration of ribavirin
- DCV + SOF with or without ribavirin was generally well tolerated
  - Low hemoglobin was observed only in patients taking ribavirin

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