All-Oral Fixed-Dose Combination Therapy With Daclatasvir/Asunaprevir/Beclabuvir, ± Ribavirin, for Patients With Chronic HCV Genotype 1 Infection and Compensated Cirrhosis: UNITY-2 Phase 3 SVR12 Results

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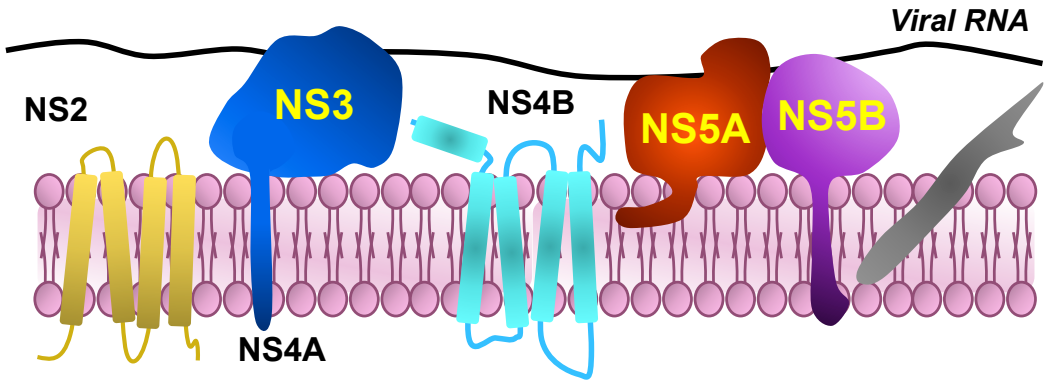
Background

- Cirrhosis can reduce response to HCV therapies – potent, well-tolerated all-oral regimens are needed
- DAA regimens, even with ribavirin, can require > 12 weeks of treatment to maximize SVR rates in patients with cirrhosis[1,2]
- Daclatasvir + asunaprevir + beclabuvir (BMS-791325) achieved SVR12 in > 92% (GT 1) or 100% (GT4) of treatment-naive patients with 12 weeks of treatment (phase 2)[3,4]
- 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

[1]Poordad F, *et al. New Eng J Med* 2014; 370:1973-1982.
[2]Afdhal N, *et al. New Engl J Med* 2014; 370:1483-1493.
[3]Everson GT, *et al. AASLD 2013*; Oral LB-1.
[4]Hassanein T, *et al. J Hepatol* 2014; 60(suppl1):S472.

All-Oral DCV-TRIO Regimen

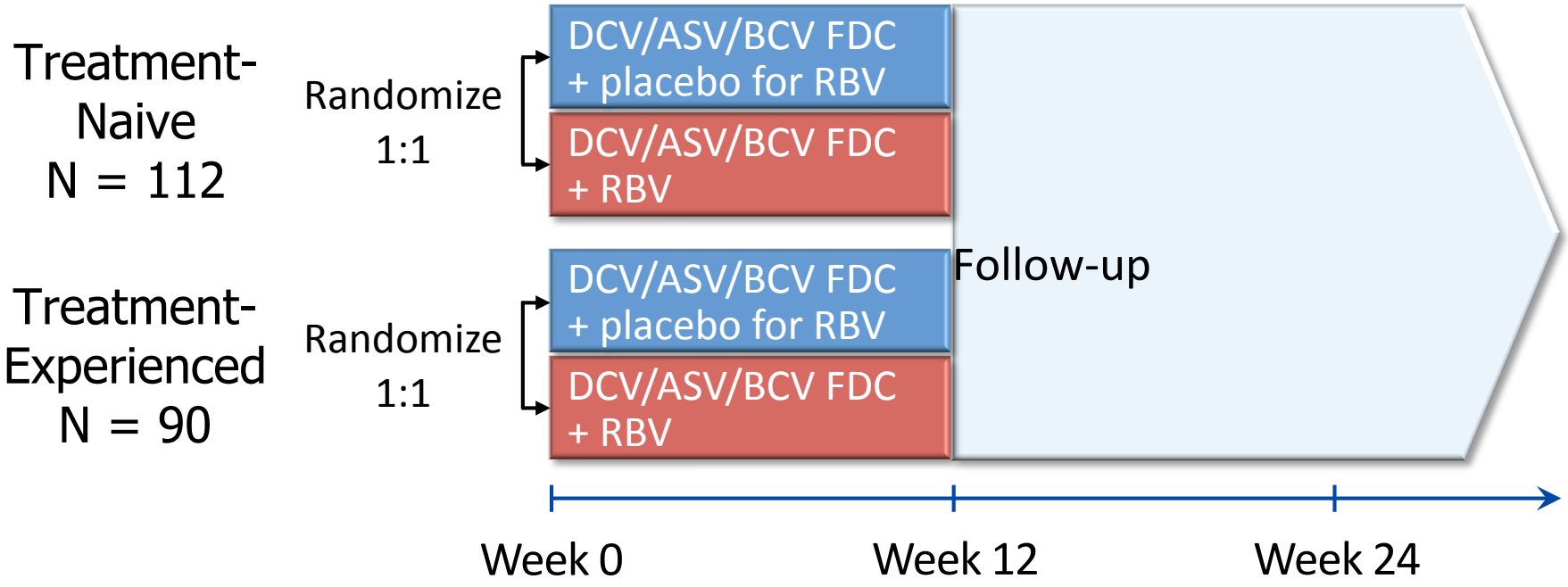
- **Daclatasvir (DCV)**
  - Pangenotypic[a] NS5A inhibitor, low potential for drug–drug interactions
  - Safe and well tolerated in > 6000 subjects
  - Approved in Europe and Japan; under regulatory review in the US
- **Asunaprevir (ASV)**
  - NS3 protease inhibitor
  - Clinical data in GT 1 and 4
-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



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

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

UNITY-2: Randomized, Double-Blind, Phase 3 Study



- Primary efficacy assessment: SVR12
  - HCV RNA < LLOQ (25 IU/mL) TD or TND at posttreatment Week 12
- Twice-daily fixed-dose combination (FDC)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg
  - With or without weight-based ribavirin twice-daily

TD, target detected; TND, target not detected

Inclusion Criteria

Patients

- Adults with GT 1a or 1b infection
- 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

- No prior exposure to IFN, RBV or any DAA or host-targeted antiviral

Treatment-Experienced

- Prior exposure to pegIFN/RBV and/or select DAAs* or host-targeted antivirals

* DAAs excluded: Prior exposure to NS5B thumb-1 inhibitors, NS3 inhibitors, or NS5A inhibitors

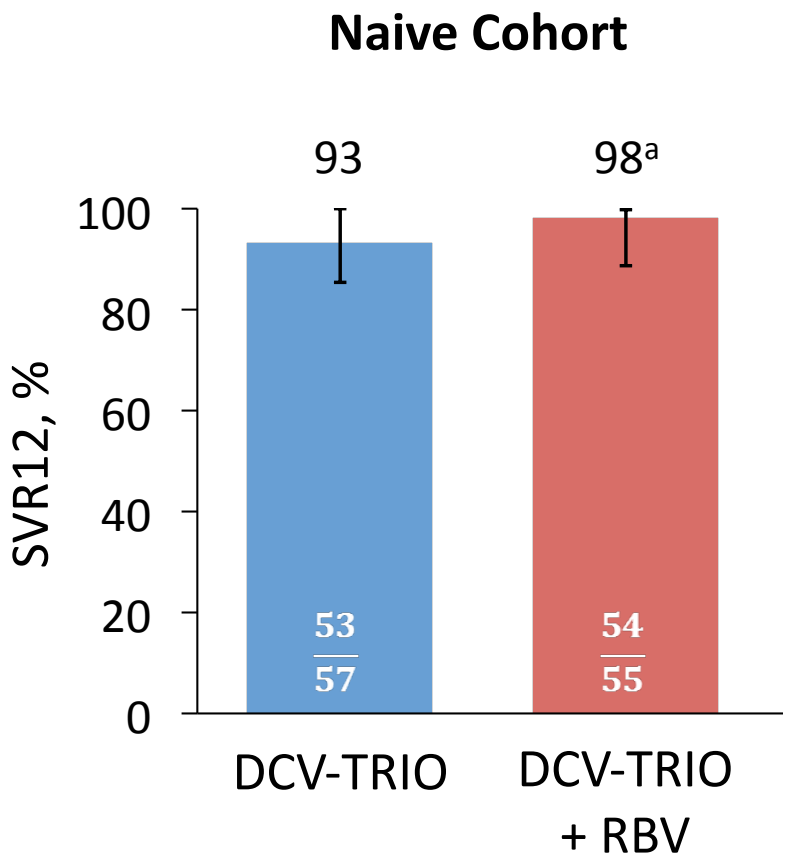
Demographic and Baseline Disease Characteristics

Parameter		Treatment-naive		Treatment-experienced	
		DCV-TRIO N = 57	DCV-TRIO+RBV N = 55	DCV-TRIO N = 45	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/Afr Amer	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	1 (2)	0	0
IL28B genotype, n (%) (rs 12979860)	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

[a]One patient (naive DCV-TRIO group) had GT 6 infection.

- Cirrhosis confirmed by liver biopsy (n = 108), Fibroscan (n = 79), or FibroTest/APRI (n = 15)
- Platelets < 100,000/mm^3 in 53 patients (26%)
- Experienced cohort (N = 90): 35 (39%) prior null responders, 8 (9%) partial responders, 16 (18%) relapsers, and 31 (34%) with other prior nonresponse

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.

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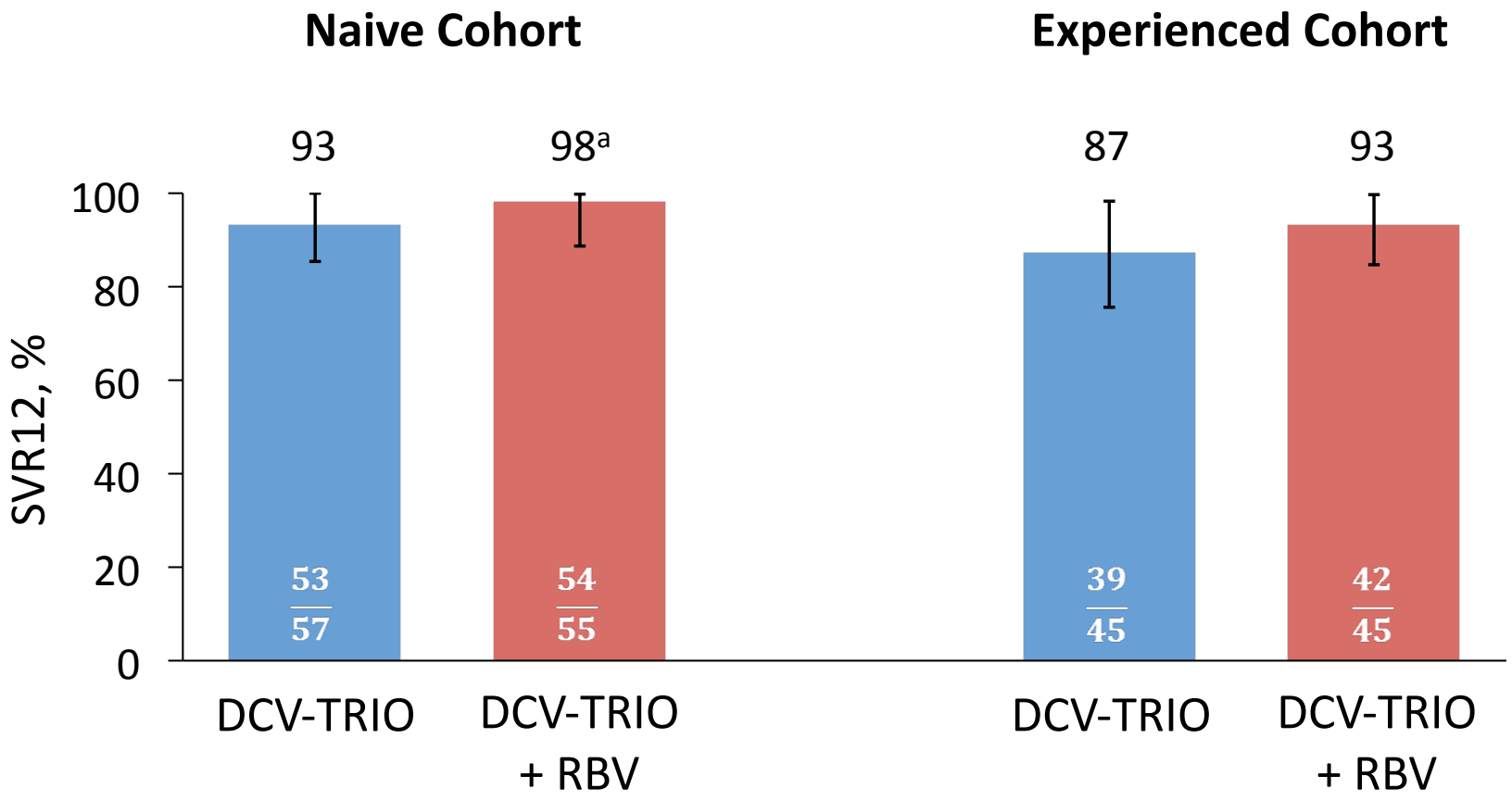

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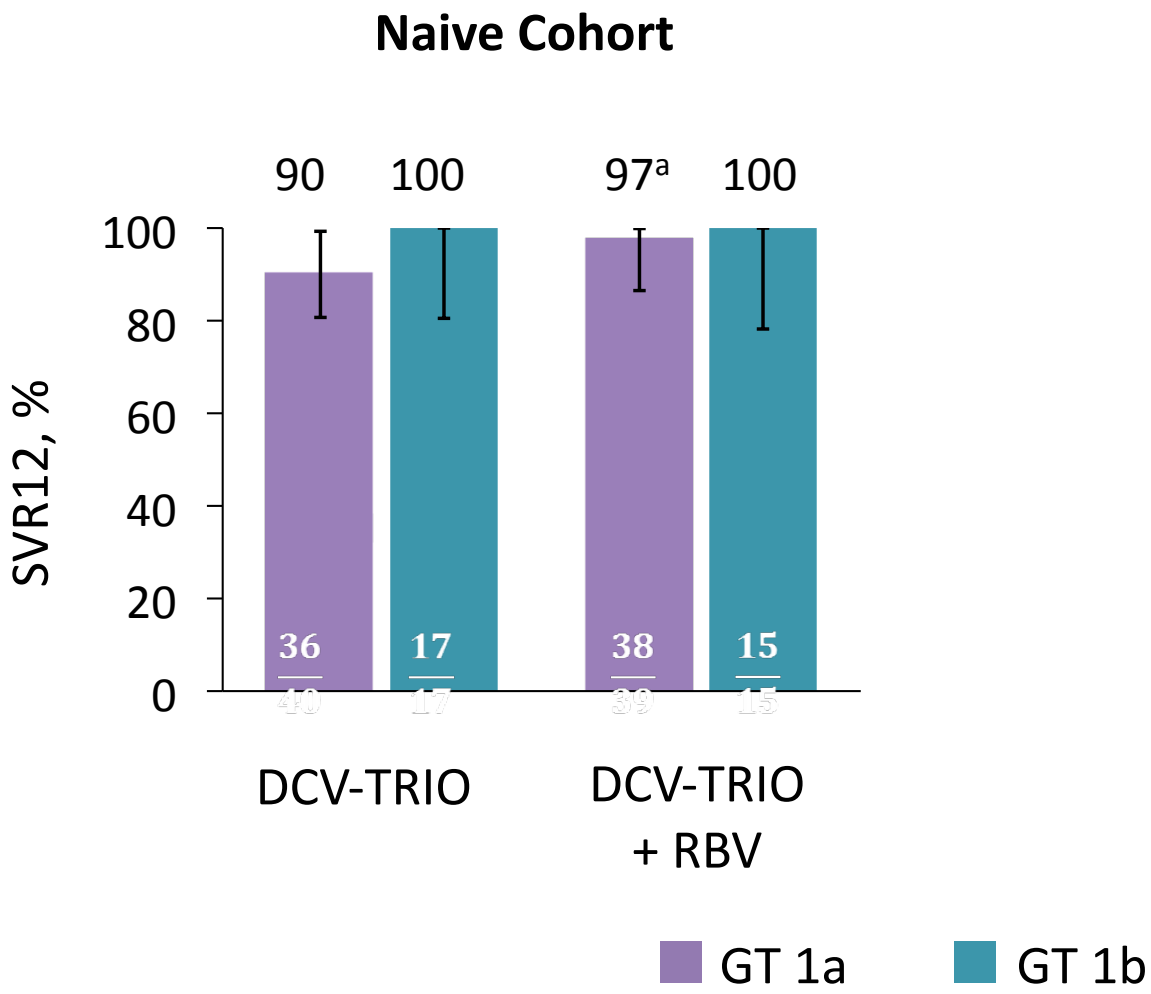
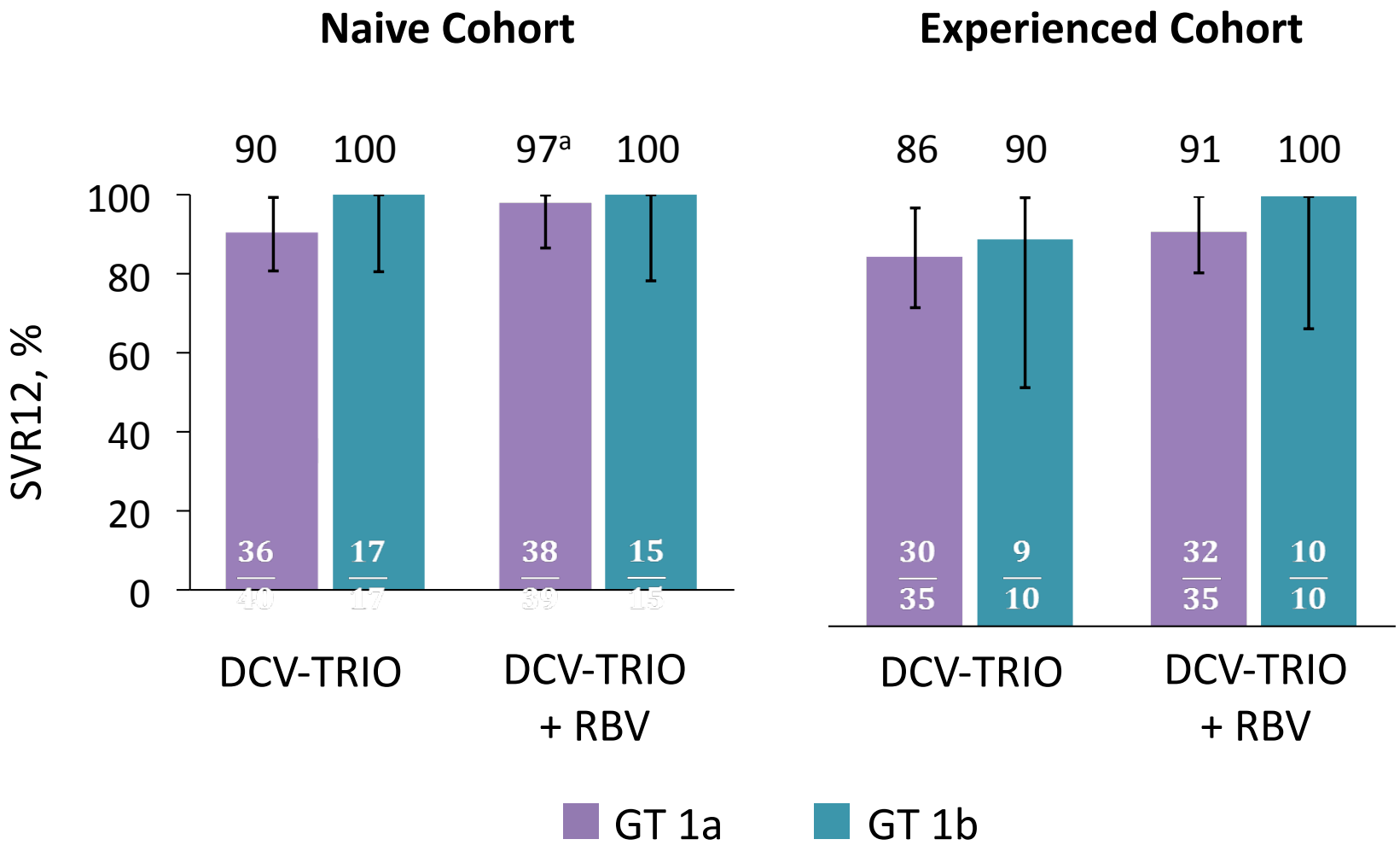
SVR12 by GT 1 Subtype



[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.

SVR12 by GT 1 Subtype



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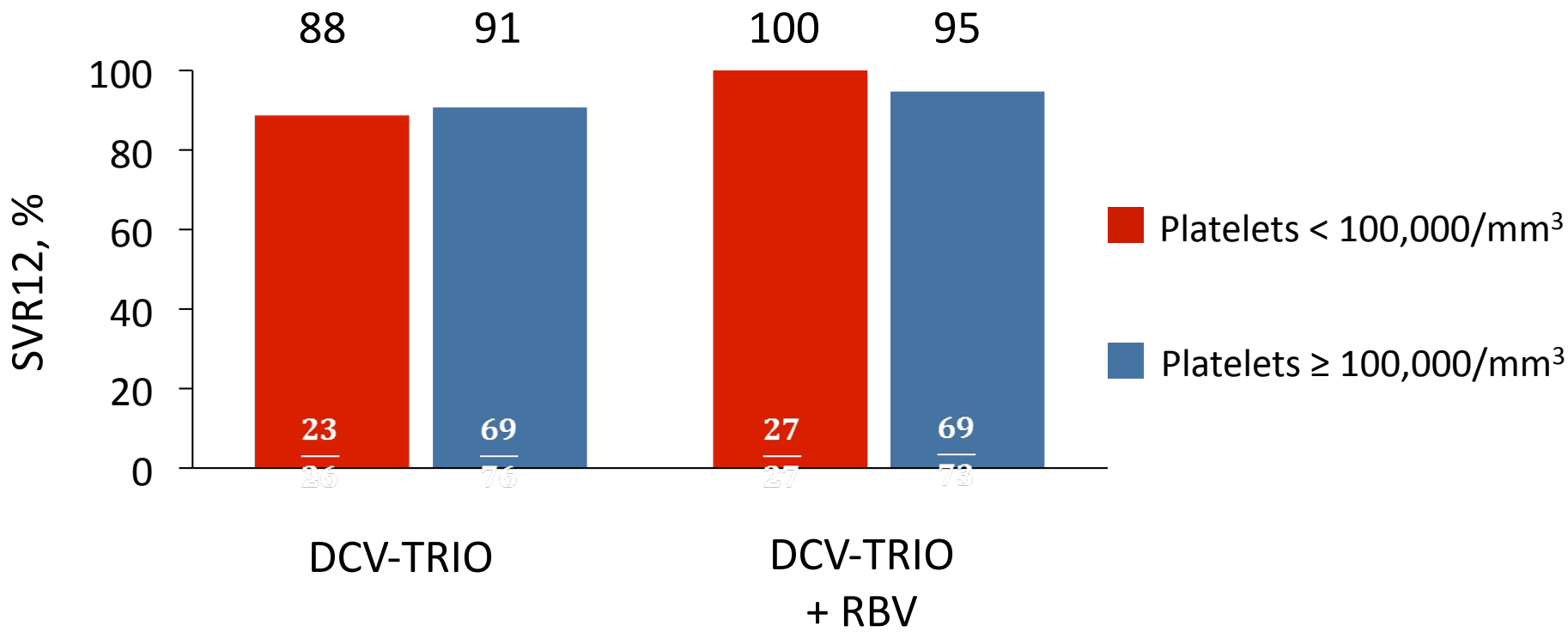
SVR12 by Baseline Platelets



- Comparable responses by gender, age, baseline HCV RNA, and *IL28B* genotype

Virologic Outcomes

Outcome, n (%)	Treatment-naive		Treatment-experienced	
	DCV-TRIO N = 57	DCV-TRIO + RBV N = 55	DCV-TRIO N = 45	DCV-TRIO + RBV N = 45
SVR12	53 (93)	54 (98)	39 (87)	42 (93)
On-treatment virologic failure	0	0	1 (2)	2 (4)
Relapse	4 (7)	0	5 (11)	1 (2)
Missing data	0	1 (2)	0	0

Resistance Analyses

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

- NS5A (28, 30, 31, 93) and NS3 (168) RAVs do 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

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Emergent RAVs in virologic failures[a]

- Sequencing data are currently available for 8 of 13 virologic failures

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	1b	Relapse	Y93H	None	None

[a] Population sequencing

Adverse Events

Event, n (%)	DCV-TRIO N = 102	DCV-TRIO + RBV N = 100
Serious AEs[a]	2 (2.0)	7 (7.0)
Discontinued RBV due to AE[b]	0	2 (2.0)
Discontinued all treatment due to AE[c]	0	1 (1.0)
AEs (any grade) in ≥ 10% of patients		
Fatigue	12 (11.8)	28 (28.0)
Headache	17 (16.7)	23 (23.0)
Nausea	14 (13.7)	17 (17.0)
Diarrhea	13 (12.7)	9 (9.0)
Insomnia	6 (5.9)	15 (15.0)
Pruritus	6 (5.9)	15 (15.0)

[a] Three SAEs considered treatment-related: anemia, ALT and total bilirubin elevations, RBV overdose.

[b] Two patients discontinued RBV due to anemia or cough; both achieved SVR12.

[c] Discontinued all study medication (due to anemia followed by ALT and total bilirubin elevations); achieved SVR12.

Laboratory Abnormalities

Treatment-Emergent Grade 3/4 Lab Abnormalities, n (%)	DCV-TRIO N = 102	DCV-TRIO + RBV N = 100
Hemoglobin < 9.0 g/dL	0	5 (5.0)
Platelets < 50 × 10^9 /L	2 (2.0)	2 (2.0)
Leukocytes < 1.5 x 10^9 /L	0	1 (1.0)
Lymphocytes < 0.5 × 10^9 /L	1 (1.0)	3 (3.0)
Neutrophils < 0.75 × 10^9 /L	1 (1.0)	1 (1.0)
ALT > 5.0 x ULN	3 (2.9)	1 (1.0)
AST > 5.0 x ULN	2 (2.0)	1 (1.0)
Total bilirubin > 2.5 x ULN	0	3 (3.0)
Total lipase > 3.0 x ULN	5 (4.9)	1 (1.0)

- One patient had concurrent ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN at Week 6 and discontinued treatment
  - Maximum values: ALT, 992 U/L; total bilirubin, 2.4 mg/dL; direct bilirubin, 1.8 mg/dL; INR, 1.55
  - Asymptomatic; lab abnormalities resolved after discontinuation of study drugs; achieved SVR12

Summary

- High SVR12 rates after 12 weeks of treatment with DCV/ASV/BCV fixed-dose combination (DCV-TRIO), with or without RBV, in patients with GT 1 and compensated cirrhosis
  - 98% in naive, 93% in experienced patients with DCV-TRIO + RBV
  - 93% in naive, 87% in experienced patients with DCV-TRIO alone
- 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

Safety and efficacy of DCV-TRIO in GT 1 non-cirrhotic patients (UNITY-1) are reported at this congress – Late-Breaker Poster LB-7

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