HEPATITIS WEB STUDY HEPATITIS C ONLINE

Daclatasvir (*Daklinza*)

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Hepatitis web study

DACLATASVIR (*DAKLINZA*)

Background Information

Hepatitis web study

Daclatasvir (*Daklinza*)

- **Approval Status**: Approved by United States FDA July 24, 2015
- **Indications and Usage**
  - Indicated with sofosbuvir, with or without ribavirin for the treatment of chronic HCV genotype 1 and 3 in adults
- **Class & Mechanism**
  - NS5A inhibitor
- **Dosing Preparations and Adjustments**
  - Daclatasvir 60 mg and 30 mg tablets
  - No dosage adjustment with any degree of renal impairment
  - No dosage adjustment with mild, moderate, or severe hepatic impairment
- **Most Common Adverse Effects**
  - Headache, fatigue, nausea, diarrhea

Source: *Daklinza* Prescribing Information. Bristol Myers Squibb

Daclatasvir (*Daklinza*) Indications and Usage

Recommended Treatment Regimen and Duration with Daclatasvir		
Genotype	**Patient Population**	**Treatment and Duration**
Genotype 1	Without cirrhosis	Daclatasvir + Sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated (Child-Pugh B or C) cirrhosis	Daclatasvir + Sofosbuvir + Ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	Daclatasvir + Sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis or Decompensated (Child-Pugh B or C) cirrhosis	Daclatasvir + Sofosbuvir + Ribavirin for 12 weeks
	Post-transplant	

Source: *Daklinza* Prescribing Information. Bristol Myers Squibb

Daclatasvir (*Daklinza*)
Estimated Cost of Therapy

Estimated Cost of Daclatasvir-Based Regimens		
Regimen	Duration	Estimated Cost*
Daclatasvir + Sofosbuvir	12 Weeks	$147,000
Daclatasvir + Sofosbuvir + Ribavirin	12 Weeks	$147,500

*Estimated cost based on Wholesaler Acquisition Cost in United States

Daclatasvir (*Daklinza*)
Adverse Effects

Adverse Reactions Reported at ≥5% Frequency, Daclatasvir + Sofosbuvir x 12 Weeks*	
Adverse Reaction^	**n (%) n = 152**
Headache	21 (14%)
Fatigue	21 (14%)
Nausea	12 (8%)
Diarrhea	7 (5%)

*Note: based in data from the ALLY-3 trial (Nelson DR, et al. Hepatology 2015;61:1127-35.)

^Transient, asymptomatic lipase elevations of greater than 3 times the upper limit of normal (ULN) were observed in 2% of subjects in ALLY-3.

Source: *Daklinza* Prescribing Information. Bristol Myers Squibb

Daclatasvir (*Daklinza*)
Drug-Drug Interactions

Drugs that are Contraindicated for use with Daclatasvir		
Mechanism of Interaction	**Clinical Comment**	**Drugs that are Contraindicated for use with Daclatasvir***
Strong induction of CYP3A by coadministered drug	May lead to loss of virologic response to daclatasvir	• **Anticonvulsants** - Phenytoin, - Carbamazepine • **Antimycobacterial agents** - Rifampin • **Herbal Products** - St. John's wort (*Hypericum perforatum*)
*Note: this table is not a comprehensive list of all drugs that strongly induce CYP3A		

Source: *Daklinza* Prescribing Information. Bristol Myers Squibb

CLINICAL TRIALS

Daclatasvir

Daclatasvir: Summary of Key Studies

- Phase 2b Trial in Treatment-Naïve GT 1 or 4
  - **COMMAND-1:** Daclatasvir + PEG/RBV
- Phase 3 Trial in Treatment-Naïve GT 4
  - **COMMAND-4:** Daclatasvir + PEG/RBV versus Placebo + PEG/RBV
- Phase 3 Trial in Treatment-Experienced GT 1 or 4
  - **HALLMARK-QUAD:** Daclatasvir + Asunaprevir + PEG/RBV
- Phase 3 Trial in Treatment-Naïve and Experienced GT 1-4 and HIV
  - **ALLY-2:** Daclatasvir + Sofosbuvir
- hase 3 Trial in Treatment-Naïve and Experienced GT 3
  - **ALLY-3:** Daclatasvir + Sofosbuvir
- Phase 3 Trial in Treatment-Naïve and Experienced GT 3
  - **ALLY-3+:** Daclatasvir + Sofosbuvir

Daclatasvir: Summary of Key Studies

- Phase 2 Trial of Treatment-Naïve or Experienced GT 1,2,3
  - **AI444040:** Daclatasvir + Sofosbuvir +/- Ribavirin
- Phase 3 Trial in Treatment-Naïve or Experienced GT 1 without cirrhosis
  - **UNITY-1:** Daclatasvir + Asunaprevir + Beclabuvir
- Phase 3 Trial in Treatment-Naïve or Experienced GT 1 cirrhotics
  - **UNITY-2:** Daclatasvir + Asunaprevir + Beclabuvir +/- Ribavirin
- Phase 3 Trial in Treatment-Naïve or Experienced GT 1B
  - **HALLMARK-DUAL:** Daclatasvir + Asunaprevir
- Phase 3 Trial in Treatment-Naïve and Experienced GT 1-4 and HIV
  - **ALLY-2:** Daclatasvir + Sofosbuvir
- Phase 3 Trial in Advanced Cirrhosis and Post-Liver Transplant GT 1-6
  - **ALLY-1:** Daclatasvir + Sofosbuvir + Ribavirin

Daclatasvir-Based Regimens in Treatment-Naïve Patients

Treatment-Naïve

Daclatasvir + Peg/RBV in Treatment-Naïve Genotype 1 or 4

COMMAND-1 Study

Hézode C, et. al. Gut. 2015;64:948-56.

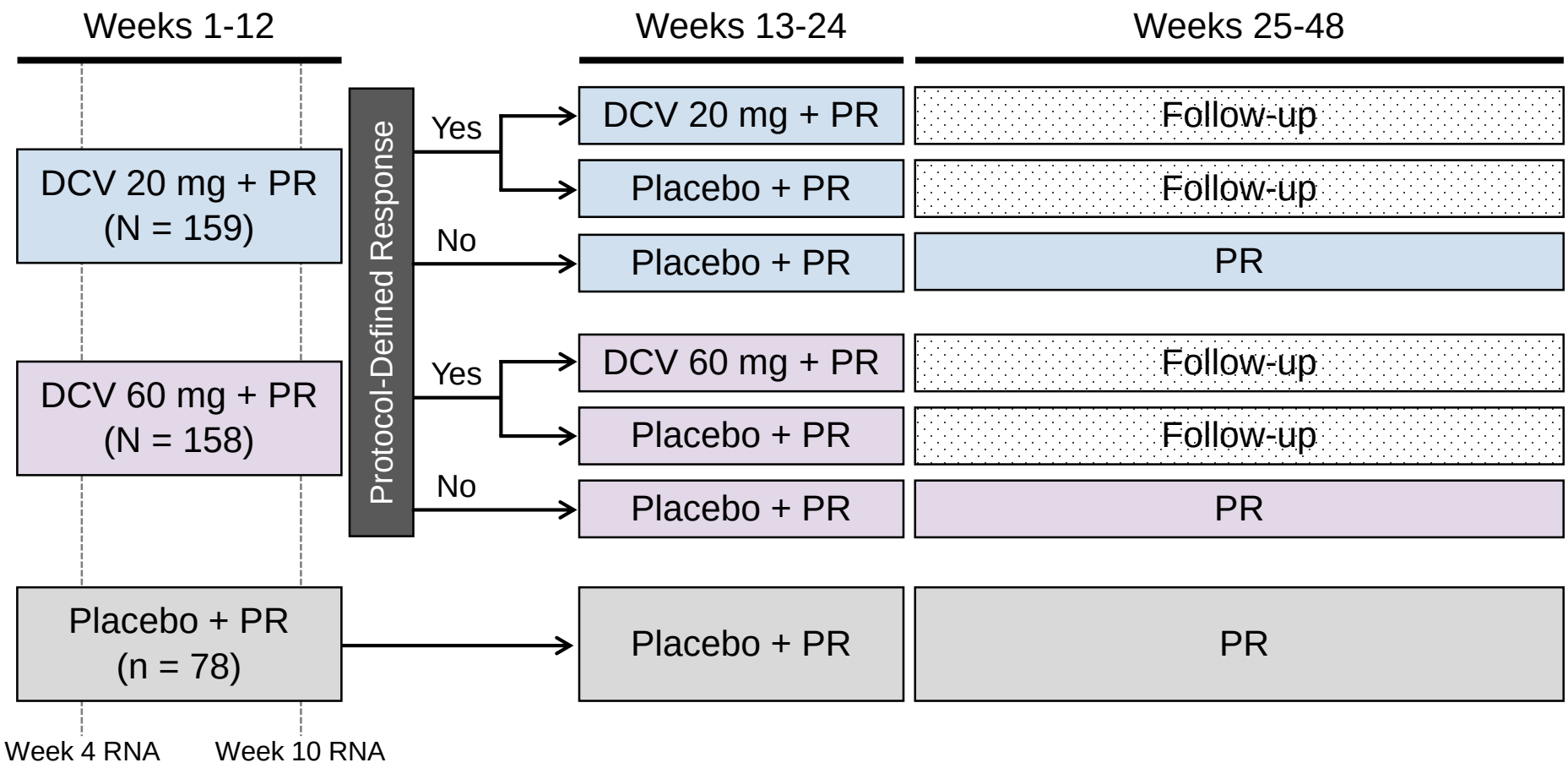
Daclatasvir + Peginterferon/RBV for HCV GT 1 or 4
COMMAND-1 Trial: Study Features

COMMAND-1 Trial: Features

- **Design**: Phase 2b randomized, double-blind placebo-controlled trial of daclatasvir (DCV) or placebo given with peginterferon alfa-2a and ribavirin in treatment-naïve patients with chronic HCV genotype 1 or 4
- **Setting**: United States and Europe
- **Entry Criteria**
  - Chronic HCV Genotype 1 or 4
  - Treatment-naïve
  - Adults 18-70
  - HCV RNA >100,000 IU/ml
  - ALT less than 5x upper limit of normal
  - Compensated cirrhosis allowed (maximum of 10% with each GT)
- **End-Points**: Primary = SVR12

Source: Hézode C, et. al. Gut. 2015;64:948-56.

Daclatasvir + Peginterferon/RBV for HCV GT 1 or 4
COMMAND-1 Trial: Design



PDR = Protocol-Defined Response (HCV RNA <lower limit of quantitation at week 4 & undetectable at week 10)
DCV = daclatasvir; PEG = peginterferon; RBV = ribavirin

Source: Hézode C, et. al. Gut. 2015;64:948-56.

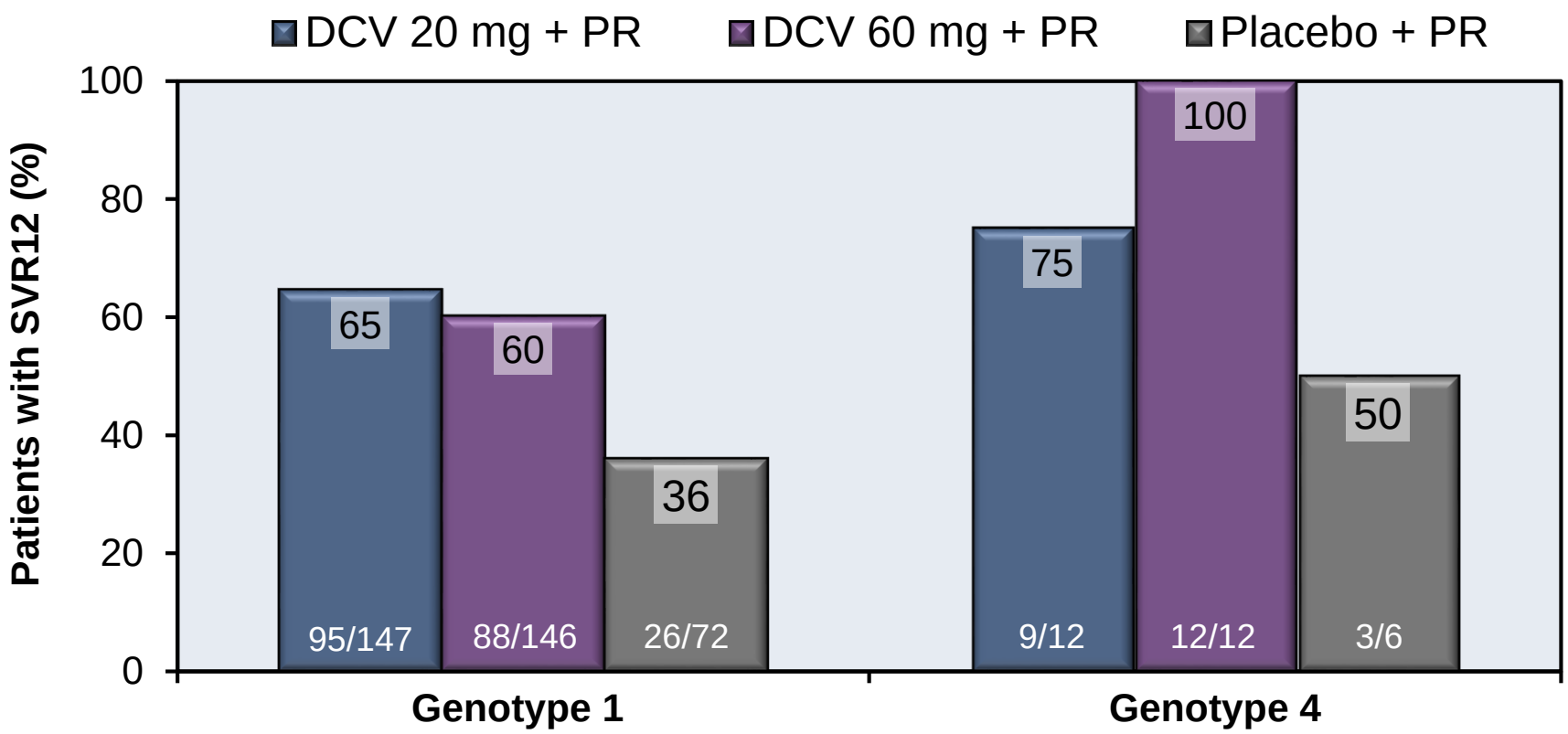
Daclatasvir + Peginterferon/RBV for HCV GT 1 or 4 COMMAND-1 Trial: Patient Characteristics

Characteristic	DCV 20 mg + PR (n=159)	DCV 60 mg + PR (n=82)	Placebo + PR (n=42)
Age, median years, years	51 (22-70)	50 (18-67)	51 (25-66)
Male %	67.3	65.2	70.5
Race, n (%) White Black Other	 132 (83.0) 15 (9.4) 12 (7.5)	 127 (80.4) 21 (13.3) 10 (6.3)	 60 (76.9) 9 (11.5) 9 (11.5)
BMI ≥30 kg/m^2, n (%)	31 (19.5)	42 (26.6)	23 (29.5)
HCV RNA, mean $\log_{10}$ IU/ml	6.5	6.5	6.4
HCV RNA ≥800,000 IU/ml, (%)	133 (83.6)	123 (77.8)	61 (78.2)
Cirrhosis present, n (%)	13 (8.2)	8 (5.1)	8 (10.3)
IL28B CC genotype, n (%)	53 (33.3)	44 (27.8)	23 (29.5)

Source: Hézode C, et. al. Gut. 2015;64:948-56.

Daclatasvir + Peginterferon/RBV for HCV GT 1 or 4
COMMAND-1 Trial: Results

SVR12, by Genotype



DCV=daclatasvir; PR=peginterferon plus ribavirin

Source: Hézode C, et. al. Gut. 2015;64:948-56.

Daclatasvir + Peginterferon/RBV for HCV GT 1 or 4
COMMAND-1: Conclusions

Conclusions: “The combination of daclatasvir/peginterferon-alfa/ribavirin was generally well tolerated and achieved higher SVR24 rates compared with placebo/peginterferon-alfa/ribavirin among patients infected with HCV genotype 1 or 4.”

Source: Hézode C, et. al. Gut. 2015;64:948-56.

Treatment-Naïve

Daclatasvir + Peg/RBV in Treatment-Naïve Genotype 4

COMMAND-4 Study

Hézode C, et. al. Antivir Ther. 2015;21:195-205.

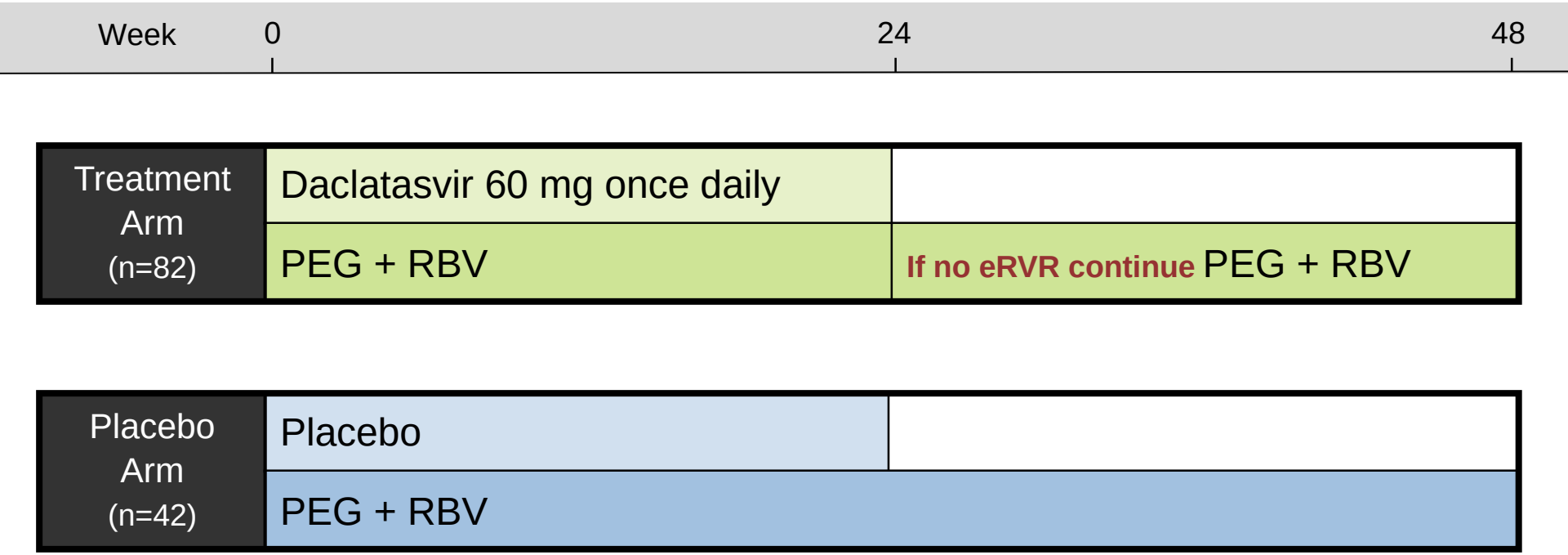
Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4 Trial: Study Features

Daclatasvir + PR Trial: Features

- **Design**: Phase 3 randomized, placebo-controlled trial of daclatasvir (DCV) with peginterferon alfa-2a and ribavirin in treatment-naïve patients with chronic HCV genotype 4
- **Setting**: United States and Europe
- **Entry Criteria**
  - Chronic HCV Genotype 4
  - Treatment-naïve
  - HCV RNA >10,000 IU/ml
  - Compensated cirrhosis allowed
- **Treatment Arm**
  - Daclatasvir with peginterferon alfa-2a and ribavirin (weight-based dosing) x 24 weeks with response-guided treatment: if extended rapid virologic response (eRVR), then treatment stopped, if no eRVR, then followed by 24-week PR tail.
- **End-Points**: Primary=SVR12

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4 Trial: Design



eRVR = HCV RNA < 25 IU/mL at weeks 4 and 12
PEG = peginterferon; RBV = ribavirin

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

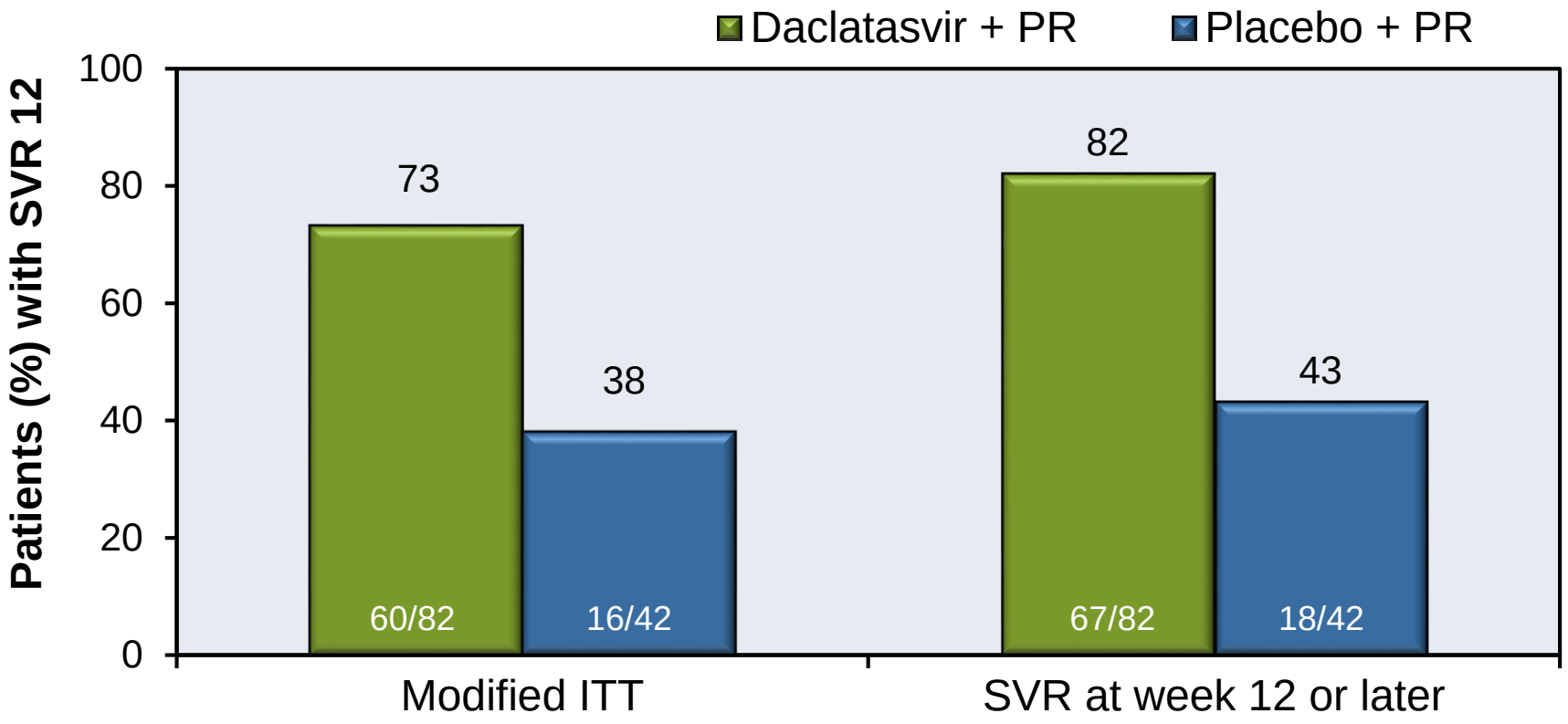
Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4 Trial: Patient Characteristics

Characteristic	DCV + Peg/RBV (n=82)	Placebo + Peg/RBV (n=42)
Male	61 (74%)	29 (69%)
Median age, years	49 (20-71)	50 (32-61)
Race White Black Other	 60 (73%) 18 (22%) 4 (5%)	 36 (86%) 5 (12%) 1 (2%)
HCV genotype 4 unspecified 4a, 4c, or 4d	 26 (32%) 46 (56%)	 16 (38%) 24 (57%)
HCV RNA ≥800,000 IU/ml	39 (48%)	16 (38%)
Cirrhosis	9 (11%)	4 (9.5%)
IL28B non-CC genotype	60 (73%)	33 (79%)

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4 Trial: Results

COMMAND-4: SVR12 by Analysis

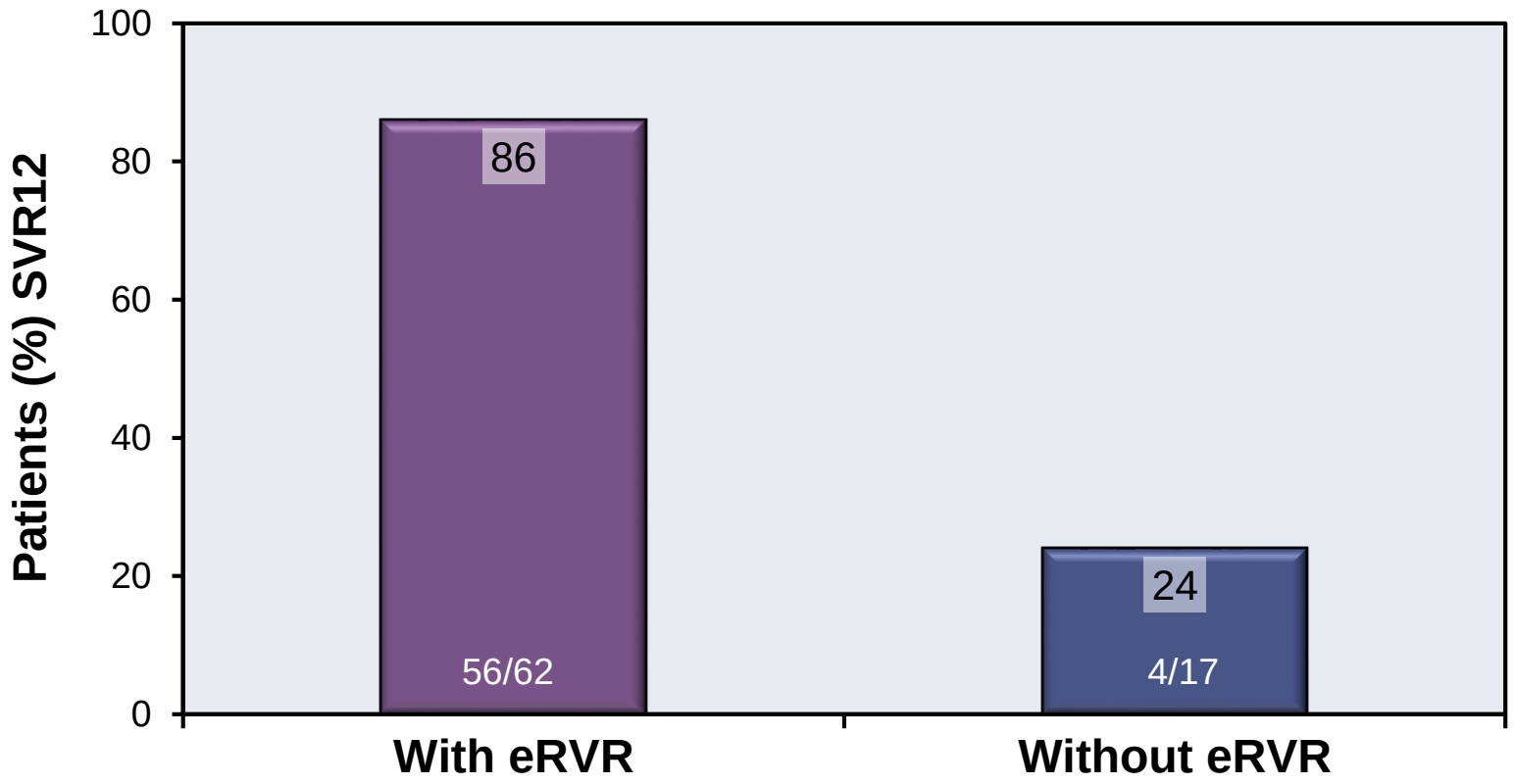


Modified ITT, intent-to-treat: patients with missing data at post-treatment week 12 were considered treatment failures.

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4: Results in Daclatasvir Arm

COMMAND-4: SVR12 by eRVR in Patients Receiving DCV



In DCV group, most (79%) patients achieved an eRVR and were eligible for shortened (24 week) duration

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

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Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4: Conclusions

Conclusions: “In treatment-naive patients with HCV GT4 infection, daclatasvir plus peginterferon/ribavirin achieved higher SVR12 rates than peginterferon/ribavirin alone. These data support daclatasvir-based regimens for treatment of HCV GT4 infection, including all-oral combinations with other direct-acting antivirals.”

Source: Hézode C, et. al. Antivir Ther. 2015;21:195-205.

Daclatasvir in Treatment-Experienced Patients

Treatment-Experienced

Daclatasvir + Asunaprevir + Peg/RBV in Genotype 1 and 4

HALLMARK-QUAD Study

Jensen D, et. al. J Hepatol. 2015;63:30-7.

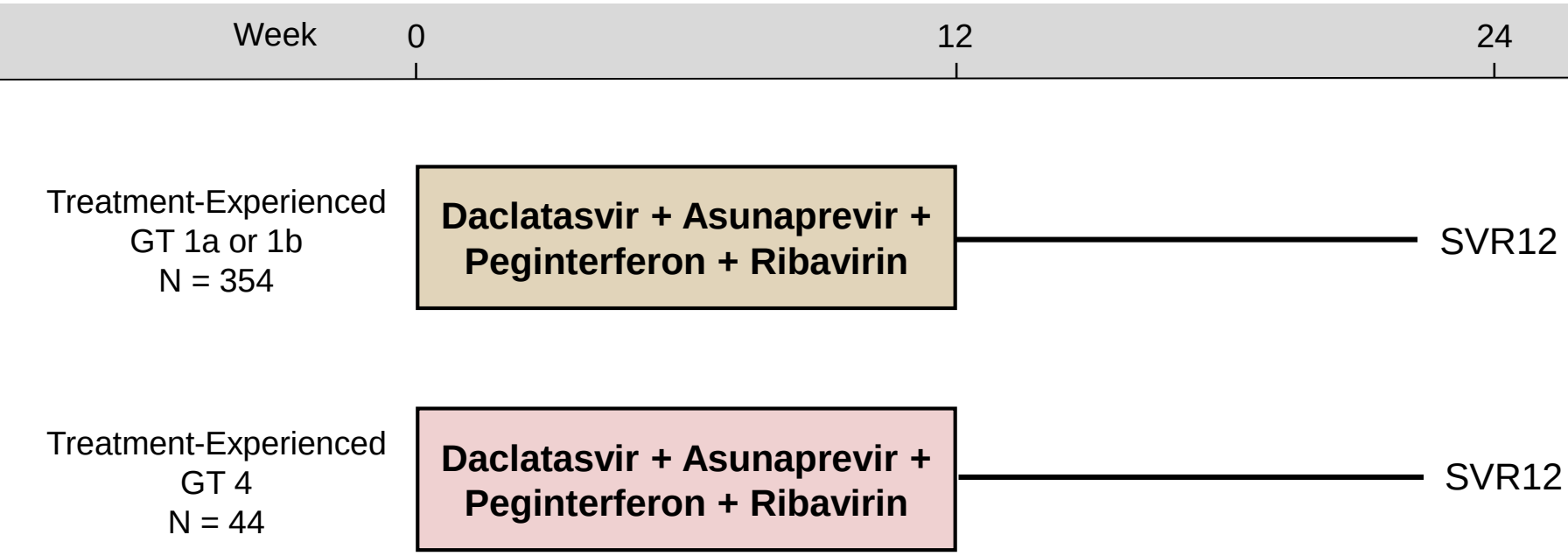
Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Study Features

Daclatasvir + Asunaprevir with Peginterferon + Ribavirin: Features

- **Design**: Phase 3 open-label single-arm study of daclatasvir (DCV) plus asunaprevir (ASV) with peginterferon alfa-2a and ribavirin in treatment-experienced, chronic HCV GT 1 or 4
- **Setting**: North & South America, Europe and Asia
- **Entry Criteria**
  - Chronic HCV Genotype 1 or 4
  - Treatment-experienced (prior null or partial responder to peginterferon + ribavirin)
  - Compensated cirrhosis allowed
- **Intervention (Single-arm)**
  - Daclatasvir plus asunaprevir with peginterferon alfa-2a and ribavirin (weight-based dosing)
- **End-Points**: Primary = SVR12

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Design



Drug Dosing
Daclatasvir: 60 mg once daily
Asunaprevir: 100 mg twice daily
Peginterferon alfa-2a: 180 mcg once weekly
Ribavirin, weight-based dosing, twice daily: 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

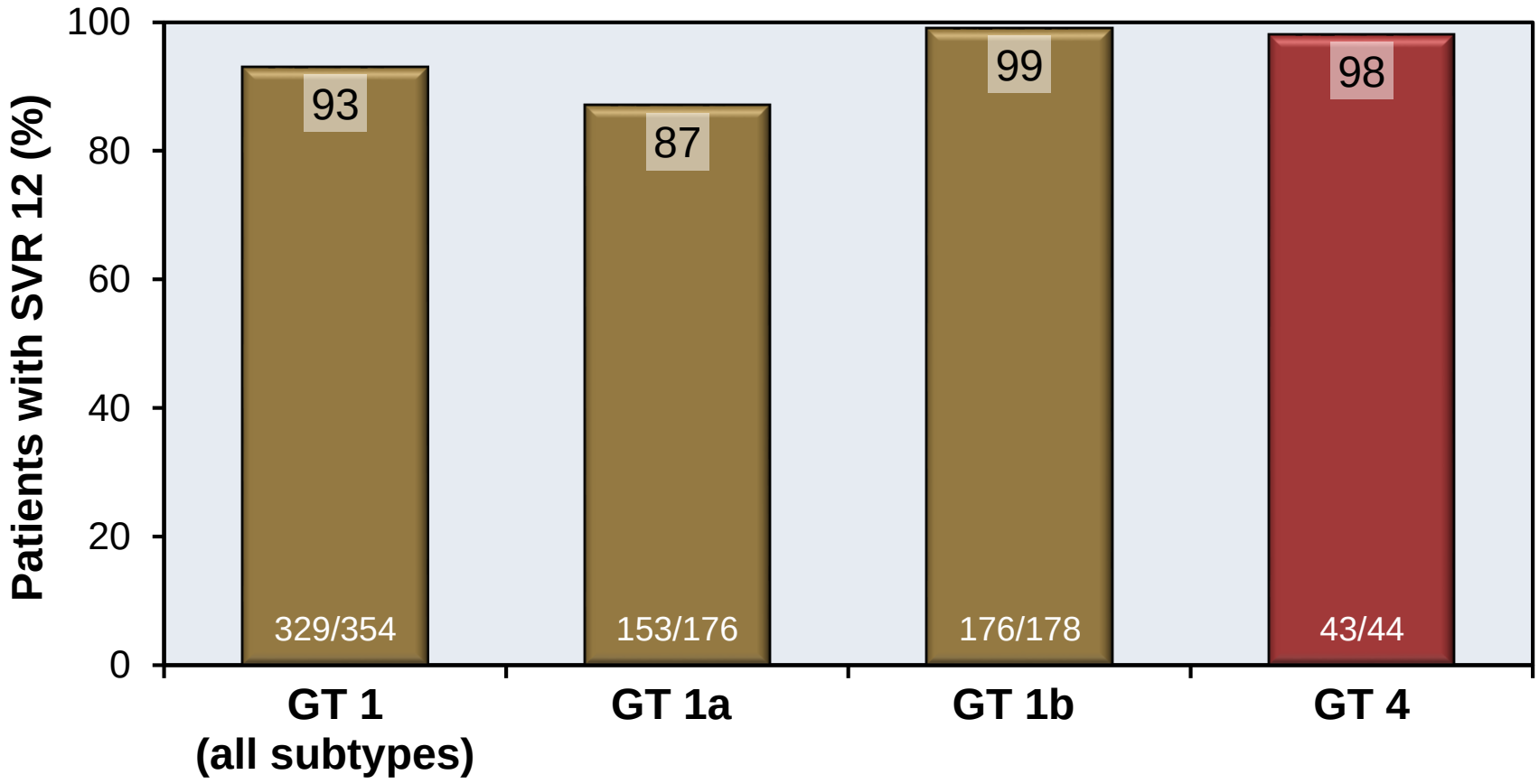
Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Patient Characteristics

Characteristic	Genotype 1 (n=354)	Genotype 4 (n=44)
Male, n (%)	240 (68%)	33 (75%)
Median age, years (range)	54 (19-76)	52 (20-71)
Race White Black Asian	 271 (77%) 33 (9%) 47 (13%)	 33 (75%) 4 (9%) 1 (2%)
HCV genotype 1a 1b	 176 (50%) 178 (50%)	N/A
HCV RNA ≥800,000 IU/ml	307 (87%)	29 (66%)
Cirrhosis	73 (21%)	20 (46%)
IL28B non-CC genotype	321 (91%)	41 (93%)
Prior treatment failure Partial response Null response	 120 (34%) 234 (66%)	 10 (23%) 34 (77%)

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Results

HALLMARK-QUAD: SVR 12 by Genotype[a]

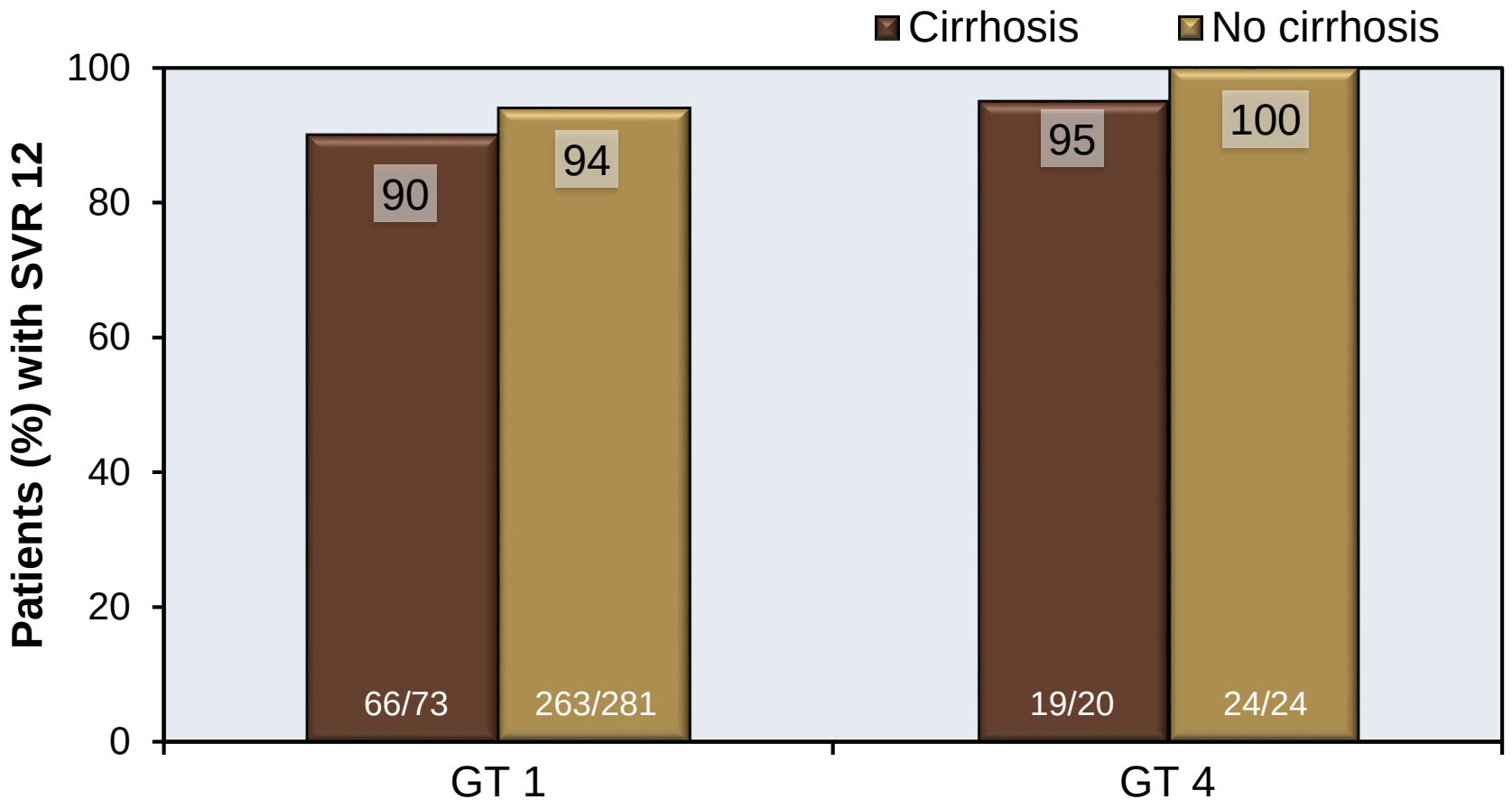


[a] Modified intention-to-treat analysis; GT = genotype

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Results

HALLMARK-QUAD: SVR12, by Cirrhosis Status



Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

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Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Adverse Events

Event	All patients (n=398)
Serious Adverse Events (AEs)	22 (6%)
AEs leading to discontinuation	18 (5%)
Adverse Events in ≥20% of patients	
Fatigue	165 (41%)
Headache	124 (31%)
Pruritus	104 (26%)
Asthenia	96 (24%)
Influenza-like illness	89 (22%)
Insomnia	89 (22%)
Rash	82 (21%)
Grade 3 or 4 Lab Abnormalities	
Hemoglobin < 9 g/dL	25 (6%)
Neutrophils < 0.75 x 10^9/L	89 (22%)
Platelets < 50 x 10^9/L	15 (4%)

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Conclusions

Conclusions: “Daclatasvir plus asunaprevir and peginterferon/ribavirin demonstrated high rates of SVR12 in genotype 1- or 4-infected prior null or partial responders. The combination was well tolerated and no additional safety and tolerability concerns were observed compared with peginterferon/ribavirin regimens.”

Source: Jensen D, et. al. J Hepatol. 2015;63:30-7.

Daclatasvir-Based Regimens in Treatment-Naïve and Treatment-Experienced Patients

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir in Genotype 3

ALLY-3 Study

Nelson DR, et al. Hepatology 2015;61:1127-35.

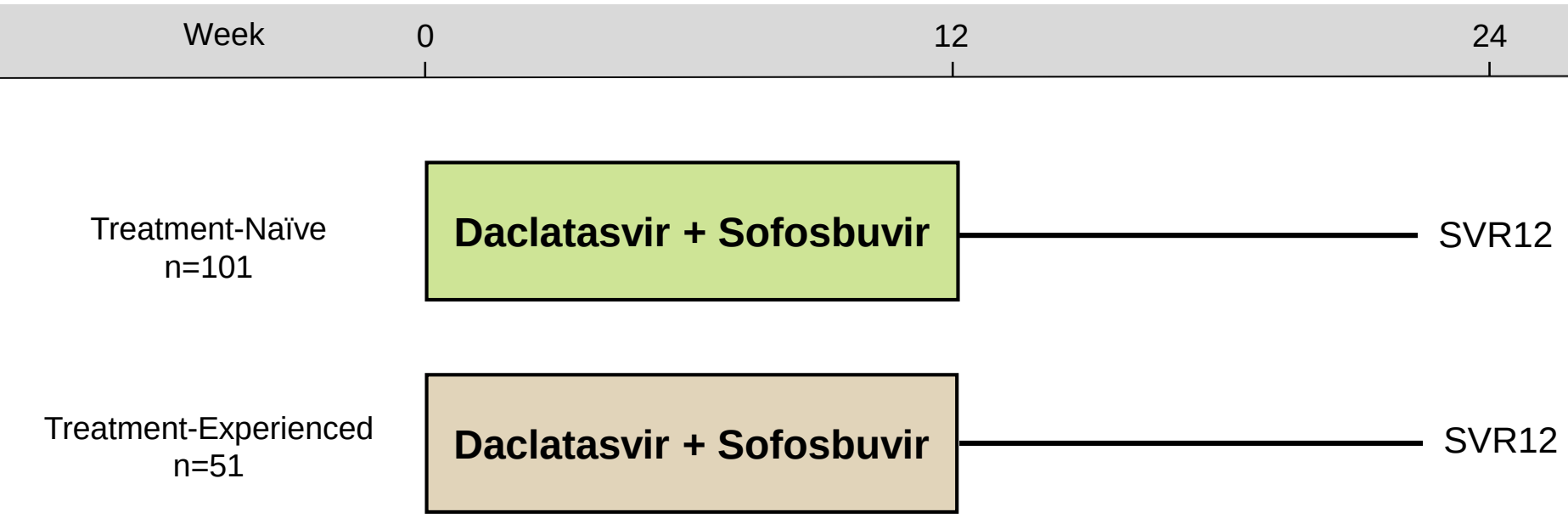
Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Study Features

Daclatasvir + Sofosbuvir Trial: Features

- **Design**: Phase 3 open-label two-cohort study of daclatasvir (DCV) plus sofosbuvir (SOF) in treatment-naïve or experienced, chronic HCV GT 3
- **Setting**: Multiple centers in the United States
- **Entry Criteria**
  - Chronic HCV genotype 3
  - Treatment-naïve or treatment-experienced (prior NS5A experience excluded)
  - HCV RNA ≥10,000 IU/ml
  - Compensated cirrhosis allowed (METAVIR F4 on biopsy, FibroScan >14.6 kPa or FibroTest (*FibroSURE*) score ≥0.75 with APRI >2)
- **Patient Groups**
  - N = 101 treatment-naïve GT3: DCV + SOF x 12 weeks
  - N = 51 treatment-experienced GT3: DCV + SOF x 12 weeks
- **End-Points**: Primary = SVR12

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Design



Drug Dosing
Daclatasvir: 60 mg once daily
Sofosbuvir: 400 mg once daily

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Patient Characteristics

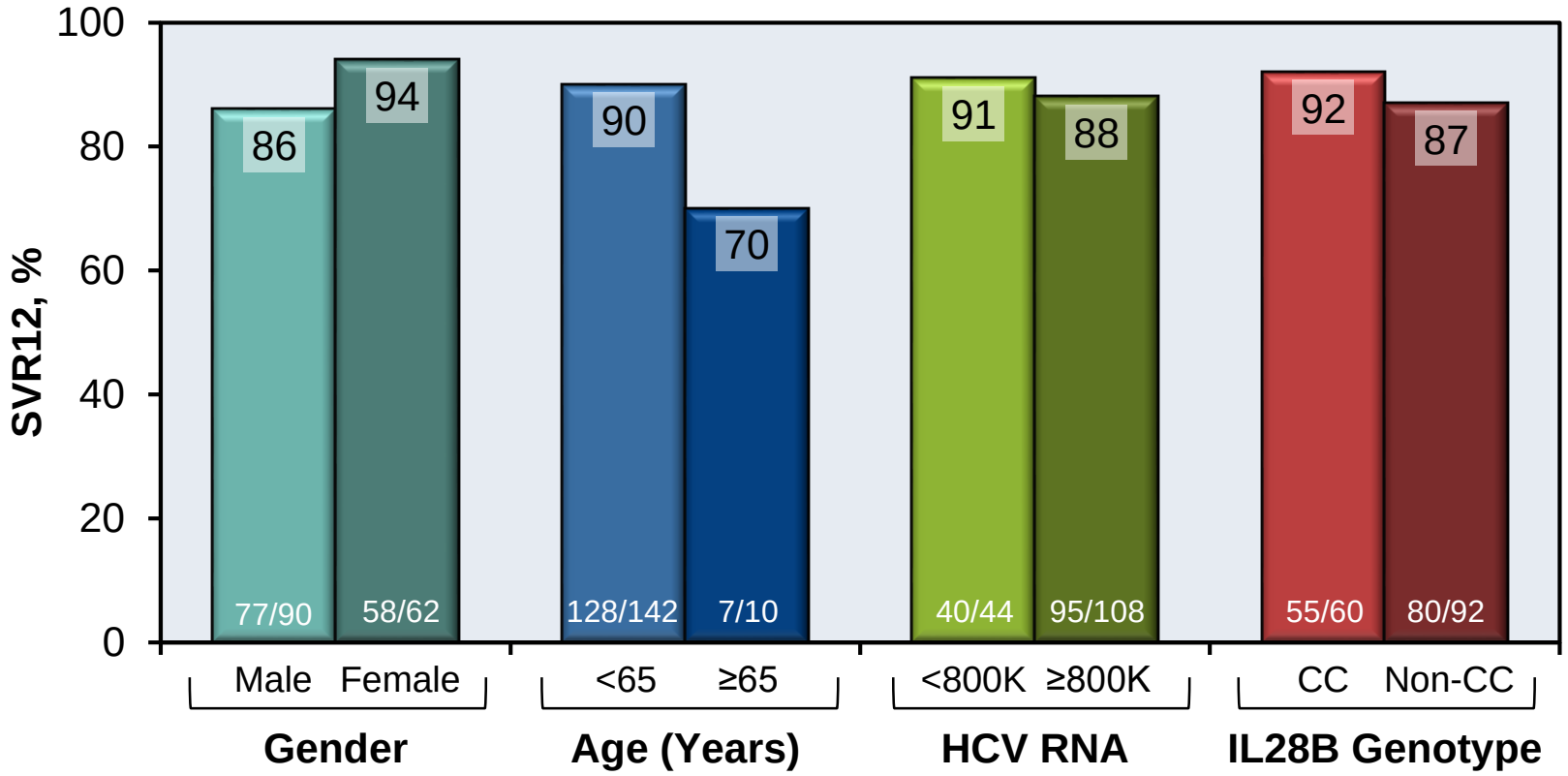
Characteristic	Treatment-Naïve (n=101)	Treatment-Experienced (n=51)
Male	58 (57%)	32 (63%)
Median age, years (range)	53 (24-67)	58 (40-73)
Race		
White	92 (91%)	45 (88%)
Black	4 (4%)	2 (4%)
Asian	5 (5%)	2 (4%)
HCV RNA ≥800,000 IU/ml	70 (69%)	38 (75%)
Cirrhosis	19 (19%)	13 (25%)
IL28B non-CC genotype	61 (60%)	31 (61%)
Prior treatment failure		
Relapse	N/A	31 (61%)
Partial response	N/A	2 (4%)
Null response	N/A	7 (14%)
Other[a]	N/A	11 (22%)

[a] Intolerant of therapy (n=6), virologic breakthrough (n=2), HCV never undetectable on treatment (n=2)

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Results

ALLY-3: SVR12, by Baseline Characteristics Status

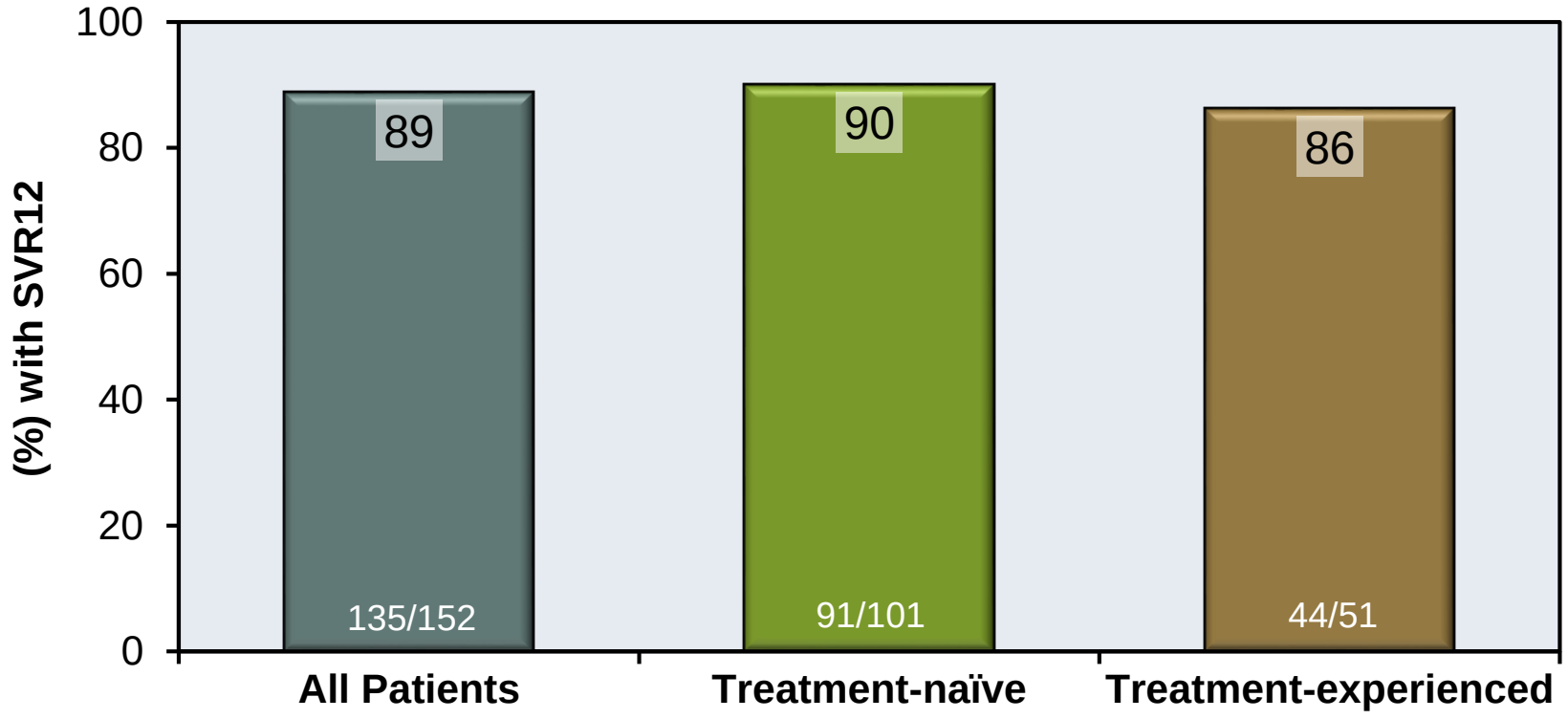


Note: SVR 12 based on HCV RNA less than lower limit of quantitation (25 IU/mL), detectable or undetectable

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Results

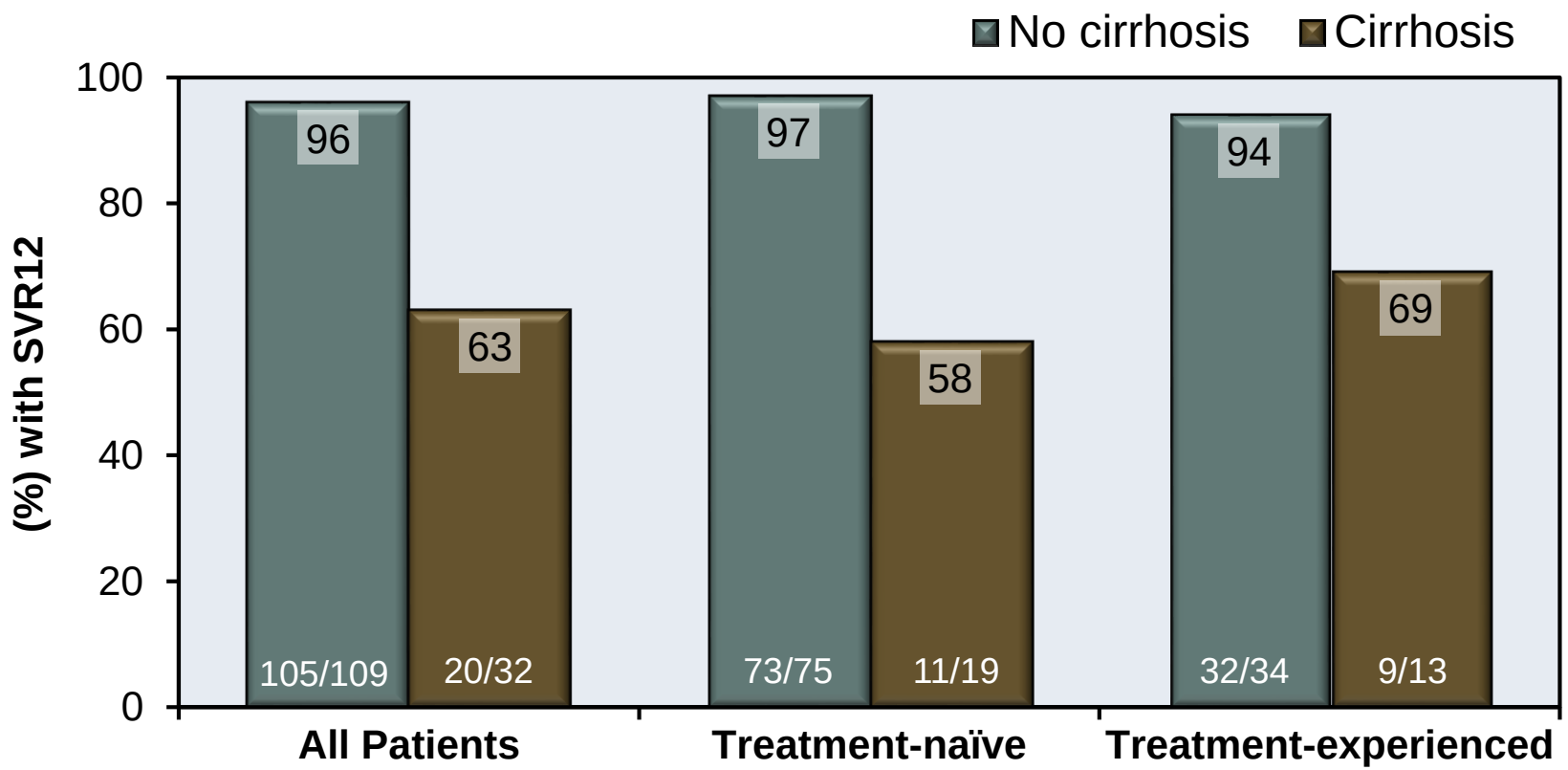
ALLY-3: SVR12, by Cirrhosis Status



Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Results

ALLY-3: SVR12, by Cirrhosis Status



Note:11 had missing or inconclusive findings for cirrhosis and not included in denominators

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Adverse Events

Event	Daclatasvir + Sofosbuvir (n=152)
Serious Adverse Events (AEs)	1 (1%)
AEs leading to discontinuation	0
Grade 3 or 4 AEs	3[a] (2%)
Adverse Events in ≥10% of patients	
Headache	30 (20%)
Fatigue	29 (19%)
Nausea	18 (12%)
Grade 3 or 4 Lab Abnormalities	
Hemoglobin < 9 g/dL	0
Neutrophils < 0.75 x 10^9/L	0
Platelets < 50 x 10^9/L	2 (1%)
Lipase > 3 x ULN	3 (2%)

[a]All were grade 3 AEs. ULN = upper limit of normal

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Conclusion

Conclusion: “A 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway.”

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir + RBV in GT3 with Advanced Liver Disease

ALLY-3+ Study

Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Study Features

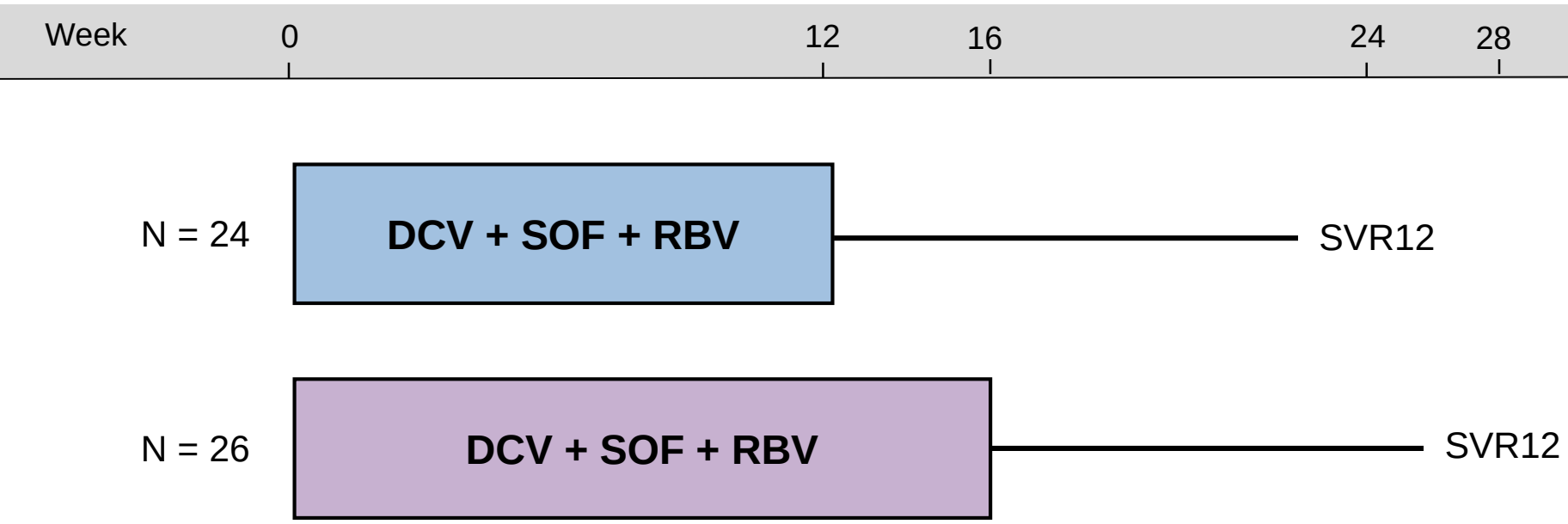
ALLY 3+ Trial: Features

- **Design**: Phase 3 open-label randomized trial of daclatasvir (DCV) and sofosbuvir (SOF) plus ribavirin (weight-based dosing) for 12 versus 16 weeks in treatment-naïve or experienced, chronic HCV GT 3 with advanced fibrosis or compensated cirrhosis
- **Setting**: 10 clinical centers in France and Australia
- **Entry Criteria**
  - Chronic HCV genotype 3
  - Treatment-naïve or treatment-experienced (prior NS5A experience excluded)
  - HCV RNA ≥10,000 IU/ml
  - Required confirmation of advanced fibrosis or compensated cirrhosis
  - Fibrosis & cirrhosis determined by liver biopsy, FibroScan, FibroTest, APRI
- **End-Points**: Primary = SVR12

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Design



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

Sofosbuvir (SOF: 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Patient Characteristics

Characteristic	12 weeks (n=24)	16 weeks (n=26)
Male	18 (75%)	22 (85%)
Median age, years (range)	53 (36-73)	56 (42-62)
Race White Asian	 23 (96%) 1 (4%)	26 (100%)
HCV RNA ≥800,000 IU/ml	20 (83%)	21 (81%)
Stage F3 (METAVIR) Compensated cirrhosis (F4)	6 (25%) 18 (75%)	8 (31%) 18 (69%)
Prior treatment status Naïve IFN-experienced SOF-experienced	 6 (25%) 15 (63%) 3 (12%)	 7 (27%) 16 (62%) 3 (11%)
DCV NS5A RAVs	7 (27%)	1 (4%)

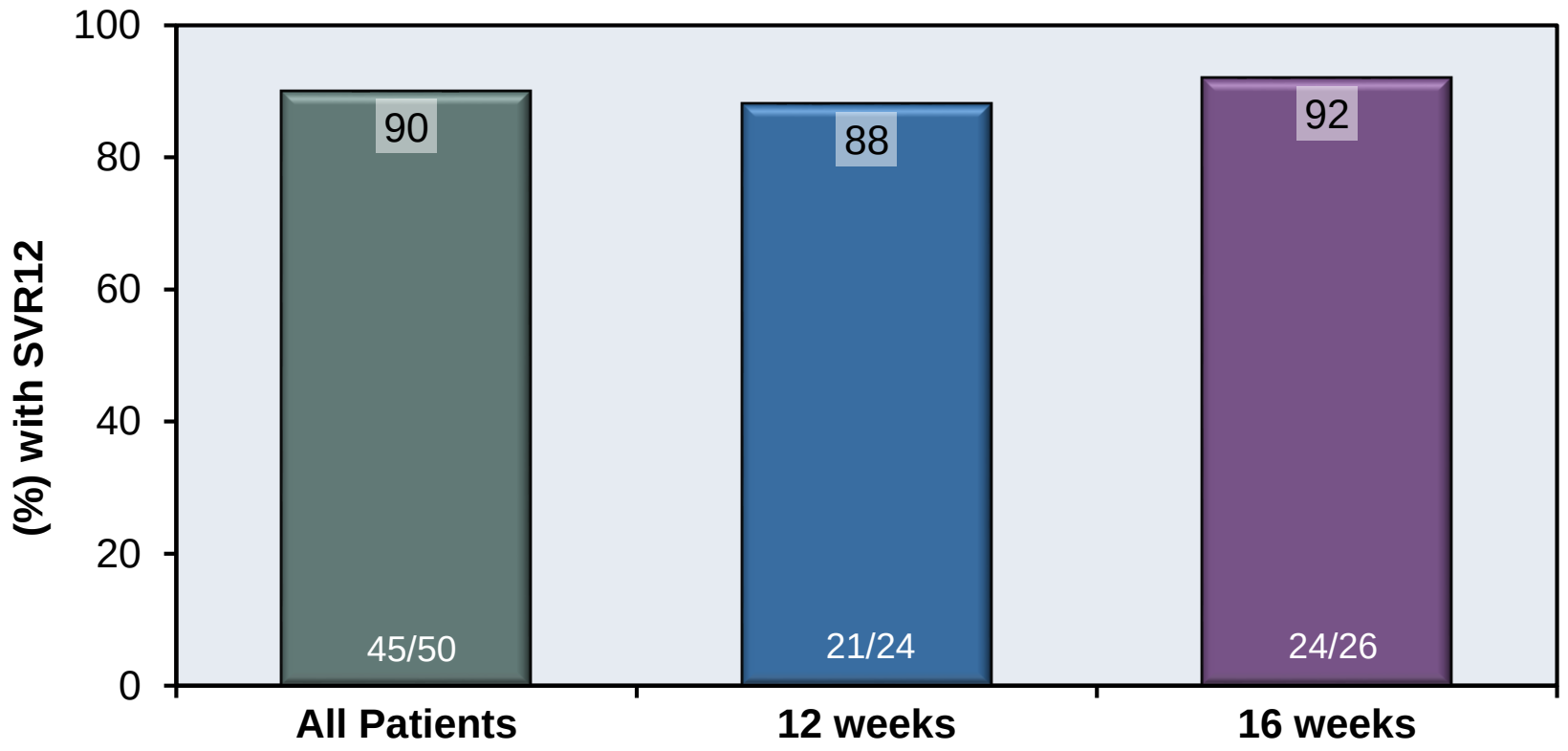
IFN=peginterferon, SOF=sofosbuvir, DCV=daclatasvir, RAVs=resistance-associated variants

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Results

ALLY-3+: SVR12 by Treatment Arm



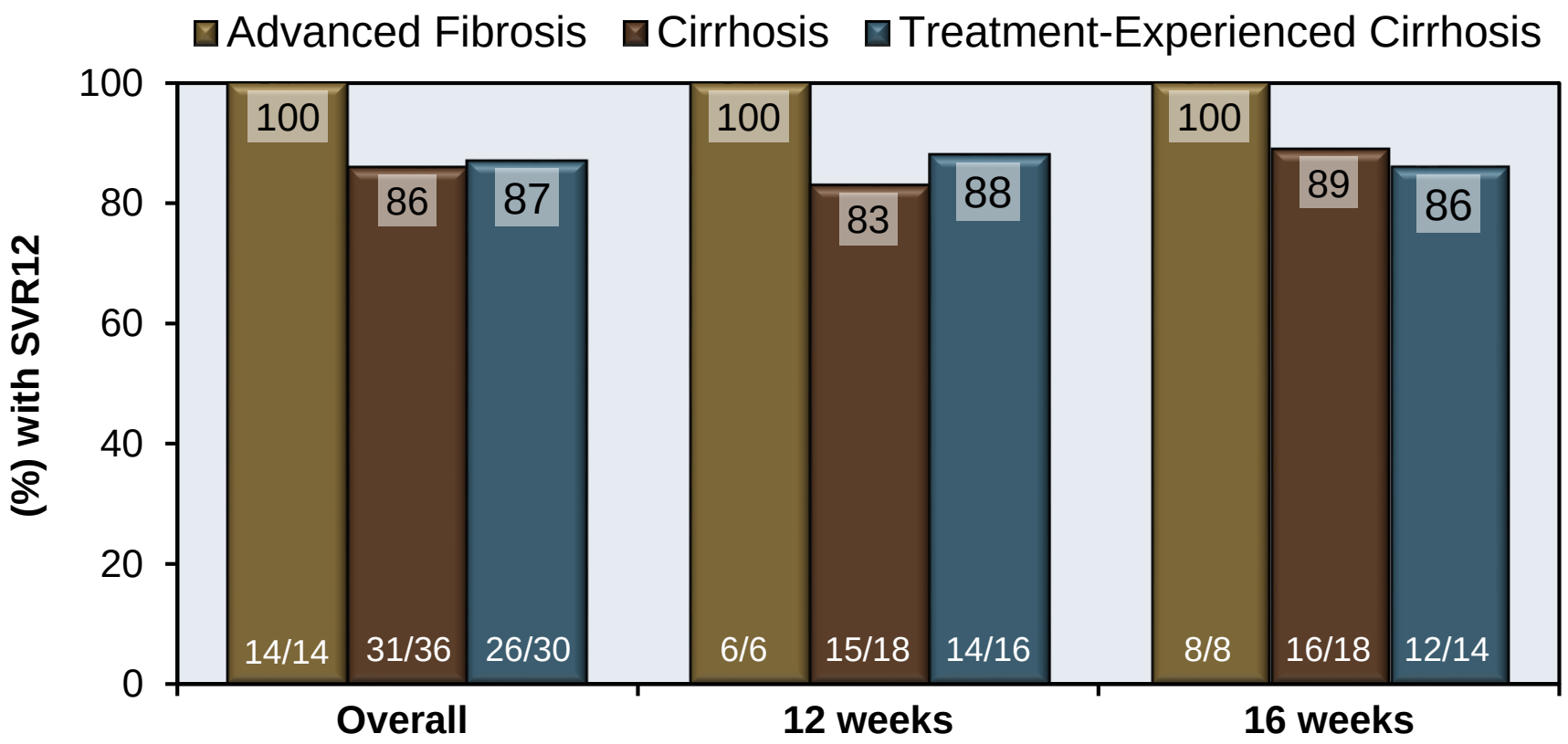
SVR12 rates determined by intent-to-treat analysis

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Results

ALLY-3+: SVR12 by Cirrhosis Status



SVR12 rates determined by intent-to-treat analysis

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Safety

Adverse Event (AE)	12 weeks (n=24)	16 weeks (n=26)
Serious AEs	2 (8%)	3 (11.5%)
AE leading to discontinuation	0	0
Ribavirin dose reduction	2 (8%)	2 (8%)
AEs in ≥10% of patients		
Insomnia	8 (33%)	7 (27%)
Fatigue	6 (25%)	7 (27%)
Headache	7 (29%)	5 (19%)
Irritability	5 (21%)	2 (8%)
Asthenia	2 (8%)	5 (19%0
Diarrhea	1 (4%)	4 (15%)
Dyspnea	2 (8%)	3 (11%)
Grade 3-4 Lab AEs		
Hemoglobin	0	1 (4%)
Total bilirubin	1 (4%)	1 (4%)

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease

ALLY-3+ Trial: Conclusion

Conclusion: “The all-oral regimen of daclatasvir-sofosbuvir-ribavirin was well tolerated and resulted in high and similar SVR12 after 12 or 16 weeks of treatment among genotype 3-infected patients with advanced liver disease, irrespective of prior HCV treatment experience.”

Source: Leroy V, et al. Hepatology 2016;63:1430-41.

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir +/- Ribavirin in Genotype 1-3 A1444040 Trial

Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

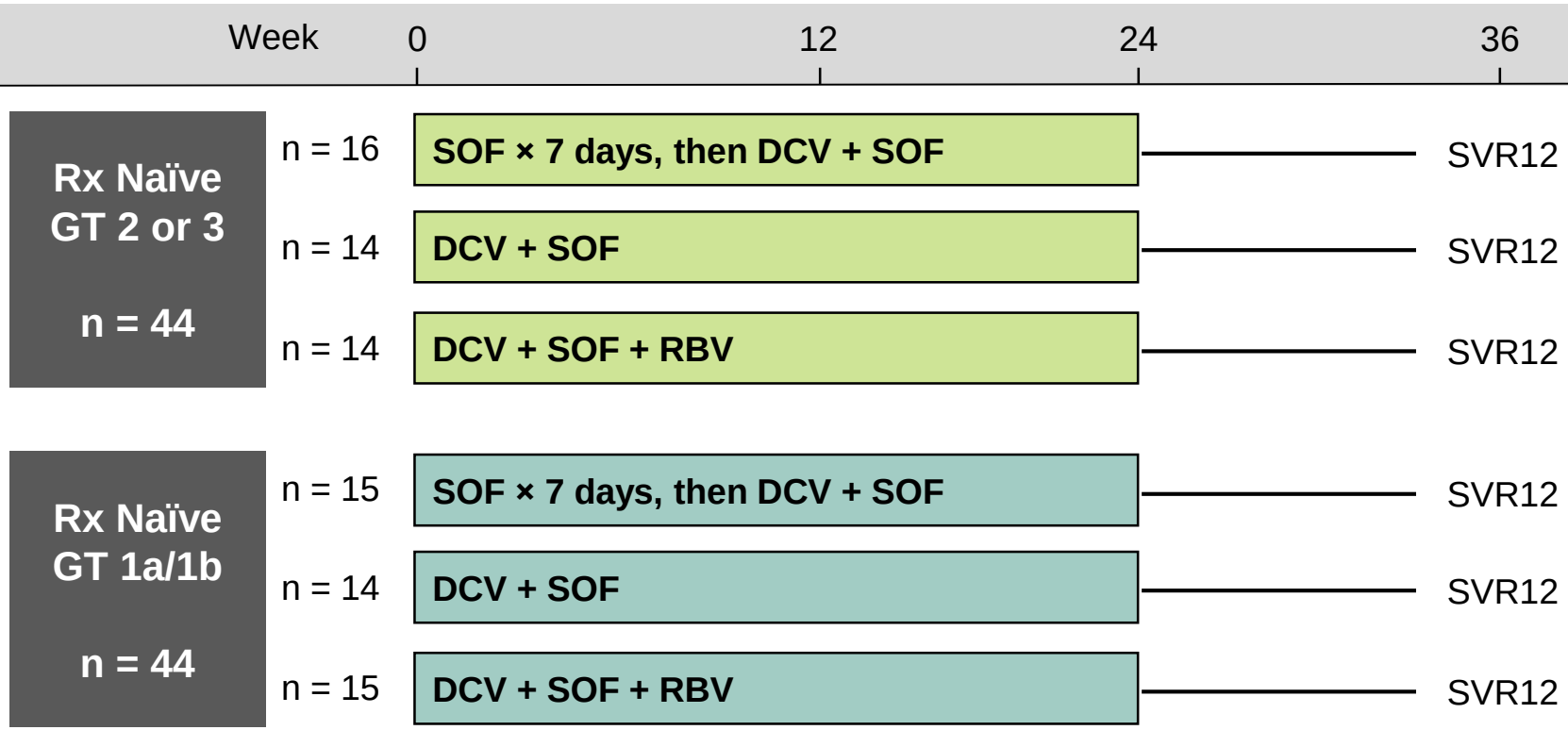
Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
A1444040 Trial: Study Features

Daclatasvir + Sofosbuvir Trial: Features

- **Design**: Randomized, open-label, phase 2a trial, using daclatasvir plus sofosbuvir with or without ribavirin in treatment naive or experienced, chronic HCV GT 1-3
- **Setting**: United States
- **Entry Criteria**
  - Chronic HCV Genotype 1, 2, or 3
  - Treatment-naïve or treatment-experienced patients
  - No evidence of cirrhosis
- **Patient Groups**
  - N = 211 total received treatment
  - N = 44 Rx naïve with GT1: DCV+ SOF +/- RBV x 24 weeks
  - N = 44 Rx naïve patients with GT 2 or 3: DCV+ SOF +/- RBV x 24 weeks
  - N = 123 Rx naïve or experienced with GT 1: DCV+ SOF +/- RBV x 12 weeks
- **End-Points**: Primary = SVR12

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
A1444040 Design: Treatment-Naïve 24 Week Rx (Part 1)



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

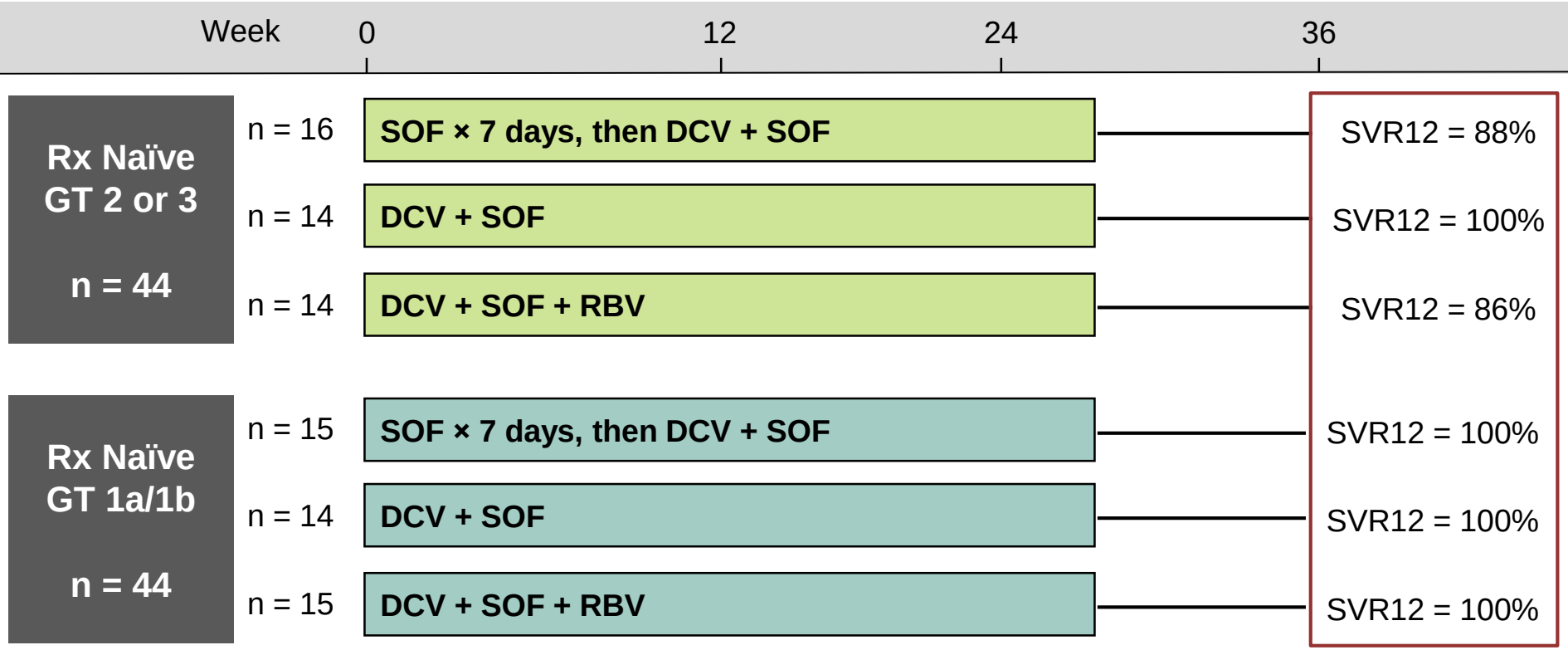
Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ribavirin (RBV): GT 2,3 (800 mg/day)

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Treatment-Naïve 24 Week Rx: Results (Part 1)



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

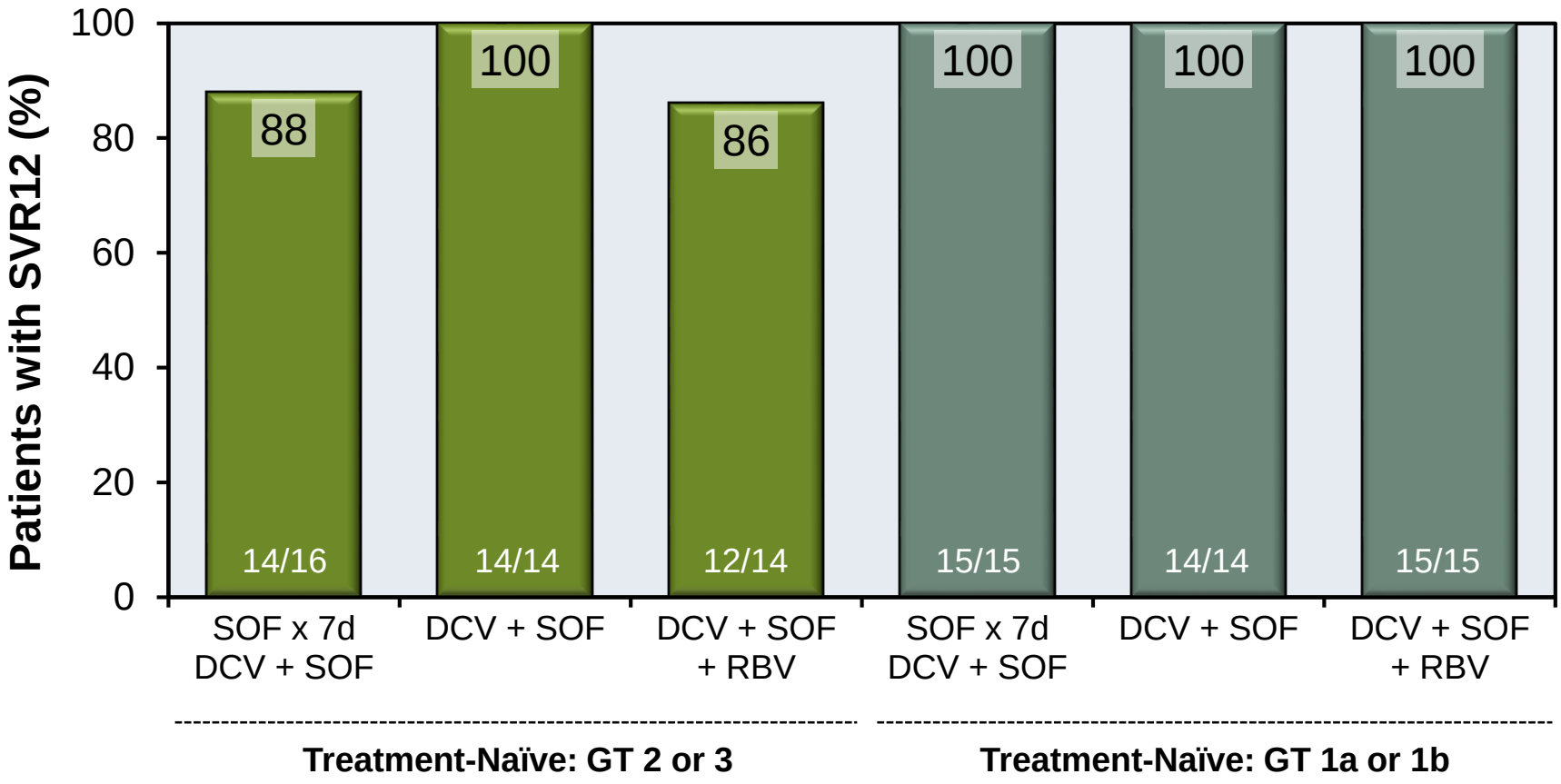
Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ribavirin (RBV): GT 2,3 (800 mg/day)

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

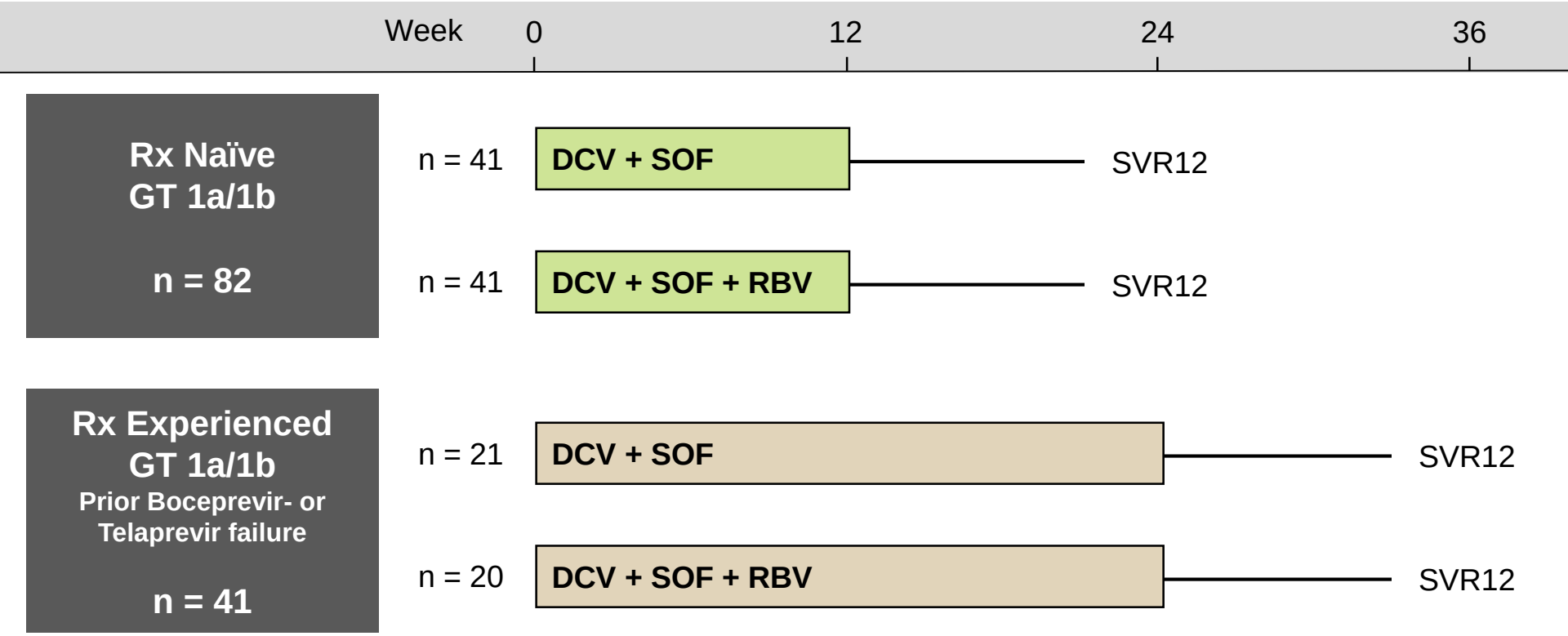
Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Treatment-Naïve 24 Week Rx: Results (Part 1)



DCV = daclatasvir; SOF = sofosbuvir; RBV = ribavirin

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
A1444040 Design: GT1 Treatment-Naïve & Experienced (Part 2)



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

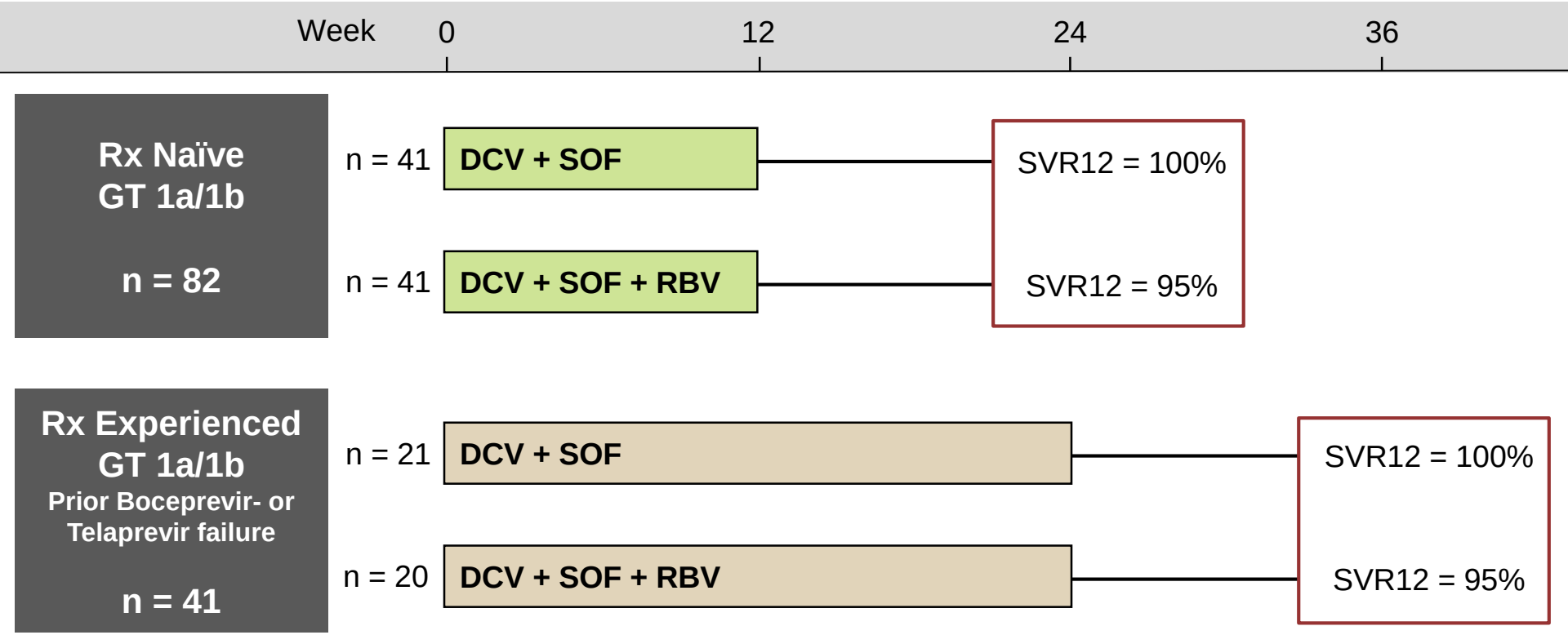
Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ribavirin (RBV): GT 2,3 (800 mg/day)

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
GT1 Treatment-Naïve & Experienced: Results (Part 2)



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

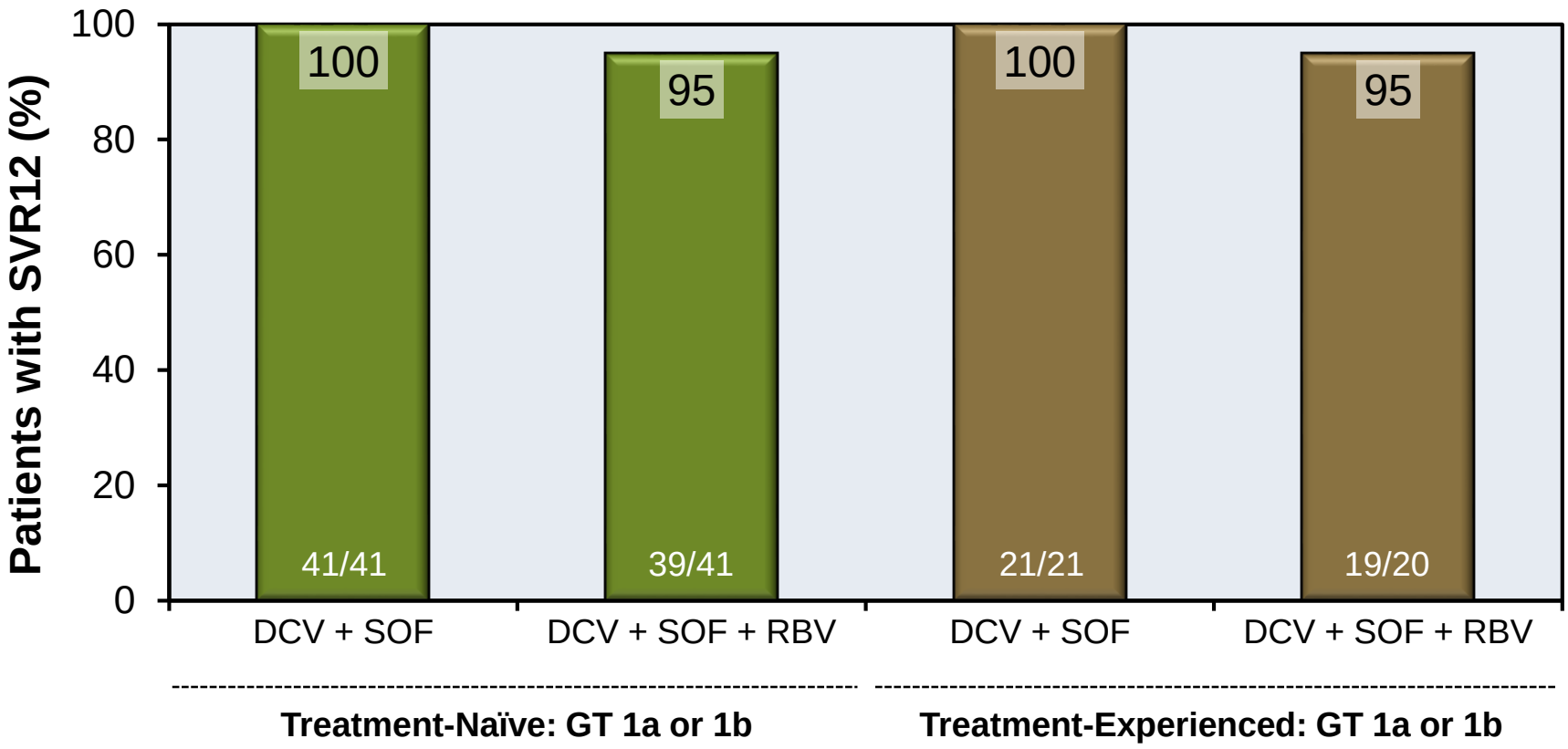
Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ribavirin (RBV): GT 2,3 (800 mg/day)

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3
GT1 Treatment-Naïve & Experienced: Results (Part 2)



DCV = daclatasvir; SOF = sofosbuvir; RBV = ribavirin

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Hepatitis web study

Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1 Trial: Conclusions

Conclusions: “Once-daily oral daclatasvir plus sofosbuvir was associated with high rates of sustained virologic response among patients infected with HCV genotype 1, 2, or 3, including patients with no response to prior therapy with telaprevir or boceprevir.”

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

Treatment-Naïve and Treatment-Experienced

Daclatasvir-Asunaprevir-Beclabuvir in GT1 Patients without Cirrhosis

UNITY-1 Study

Poordad F, et al. JAMA 2015;313:1728-35.

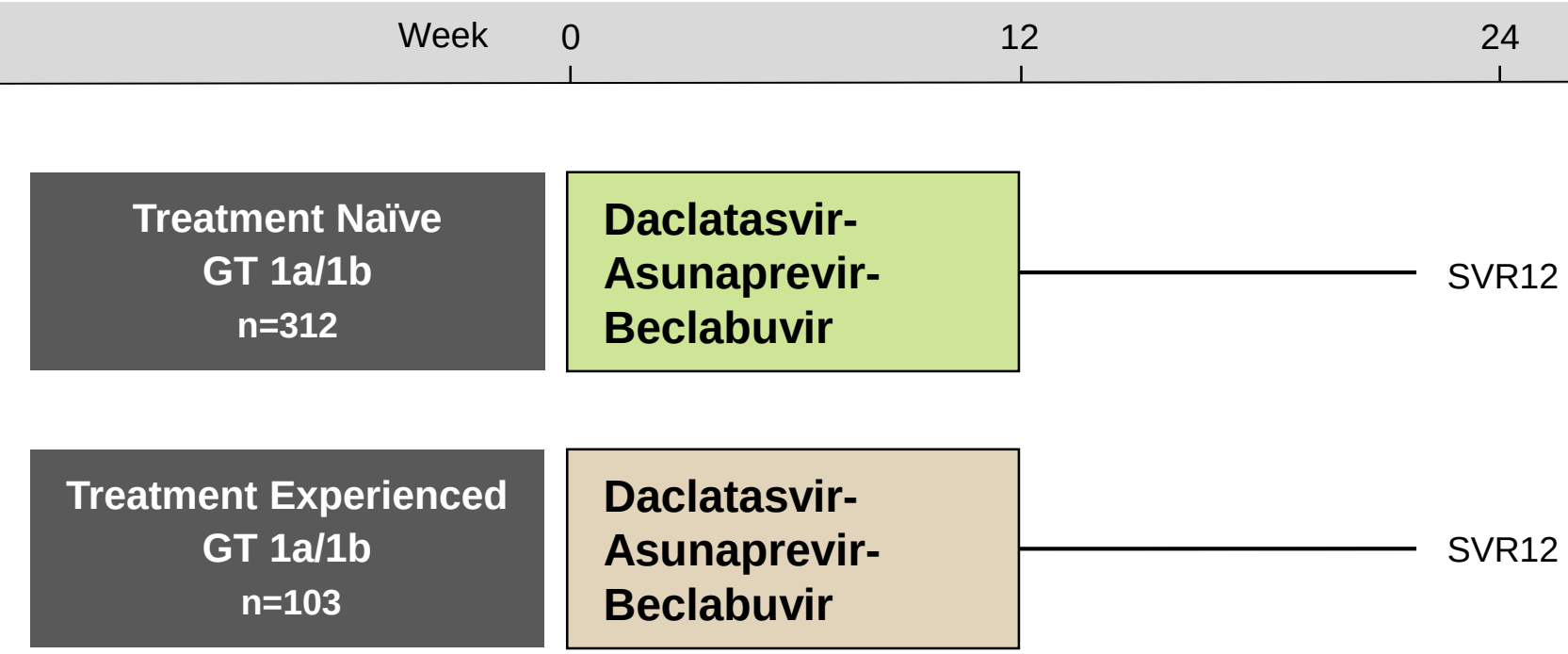
Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Study Features

Daclatasvir-Asunaprevir-Beclabuvir Trial: Features

- **Design**: Multicenter, open-label single-arm phase 3 trial of daclatasvir-asunaprevir-beclabuvir (fixed-dose combination) +/- ribavirin in treatment-naïve or experienced, chronic HCV GT 1 patients without cirrhosis
- **Setting**: Multiple centers in the United States, Canada, Australia, France
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - No cirrhosis
  - Treatment-naïve or treatment-experienced
  - HCV RNA ≥10,000 IU/ml
- **End-Points**: Primary = SVR12

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Study Design



Drug Dosing

Daclatasvir-Asunaprevir-Beclabuvir (30/200/75 mg): fixed dose combination BID

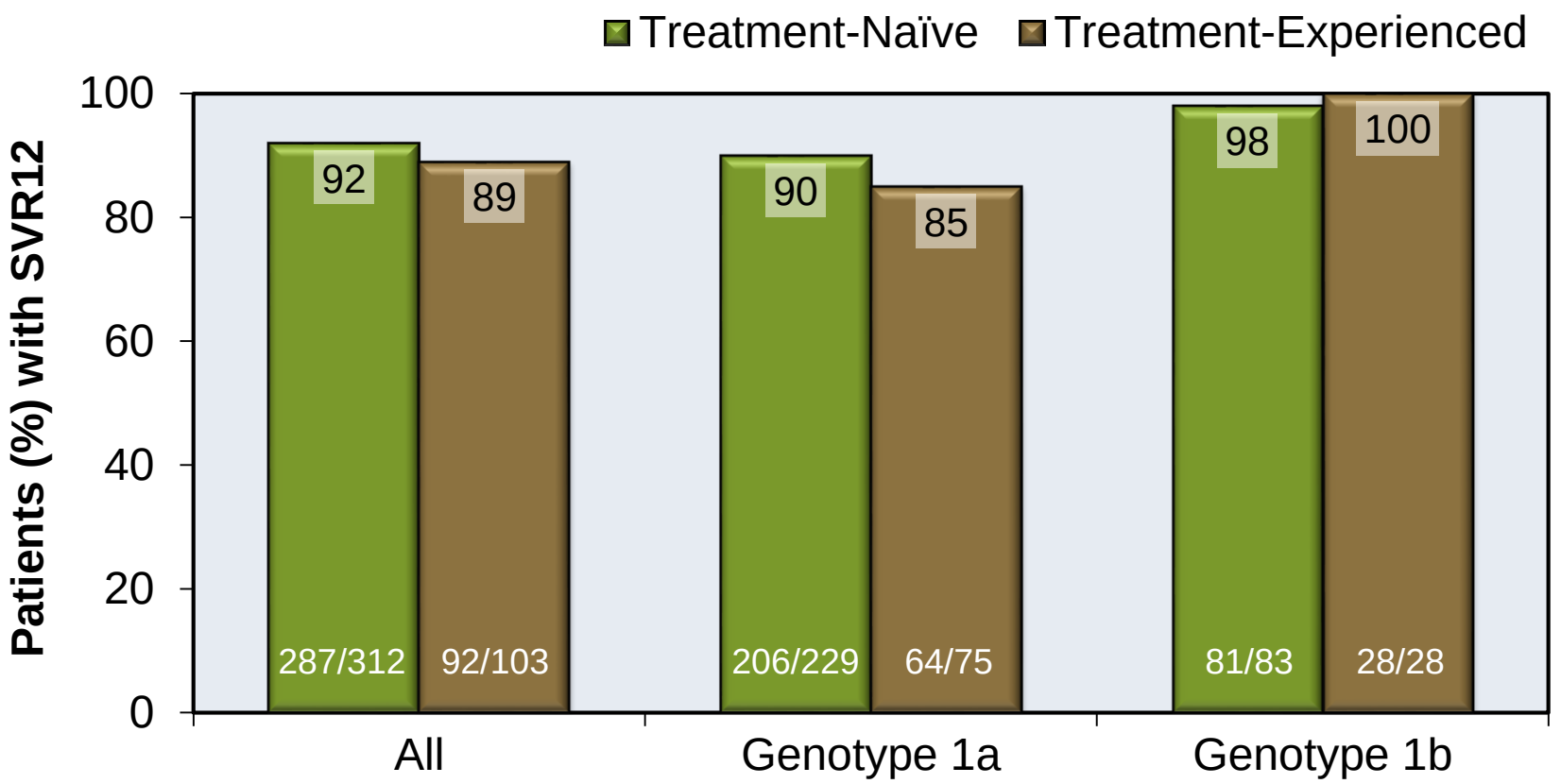
Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Patient Characteristics

Characteristic	Treatment-Naïve (n=312)	Treatment-Experienced (n=103)
Male	175 (56%)	64 (62%)
Median age, years (range)	54 (19-77)	57 (22-69)
Race White Black Asian	 270 (87%) 34 (11%) 9 (2%)	 91 (88%) 7 (7%) 2 (2%)
HCV RNA ≥800,000 IU/ml	244 (78%)	93 (90%)
HCV subtype 1A	229 (73%)	75 (73%)
IL28B non-CC genotype	221 (71%)	87 (85%)
Prior treatment failure Relapse Partial response Null response Interferon intolerant	 N/A N/A N/A N/A	 39 (38%) 12 (12%) 25 (24%) 7 (7%)

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Results



DCV = daclatasvir; ASV = asunaprevir; BCV = beclabuvir

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Virologic Failure

- Virologic failure occurred in 34 patients (8%): 32 of whom had genotype 1A infection.
- Among GT1A patients who failed, NS5A resistance-associated variants (RAVs) emerged in 30/31 (97%) patients
  - Q30 most common substitution
- NS3 protease RAVs emerged in 29/31 (94%) genotype 1A patients
  - R155 most common substitution
- NS5B RAVs emerged in 12 of 31 (39%) genotype 1A patients
  - P495 most common substitution

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Adverse Events

Event	Total Patients (n=415)
Serious Adverse Events (AEs)	7 (2%)
AEs leading to discontinuation	3 (1%)
Adverse Events, ≥10% incidence	
Headache	107 (26%)
Fatigue	69 (17%)
Diarrhea	58 (14%)
Nausea	56 (14%)
Grade 3 or 4 Lab Abnormalities	
Hemoglobin < 9 g/dl	0
Neutrophils < 0.75 x 10^9/L	2 (0.5%)
ALT >5 x ULN	19 (5%)
AST >5 x ULN	9 (2%)
Bilirubin, total > 2.5 x ULN	0
Lipase, total > 3 x ULN	16 (4%)

ULN = upper limit of normal

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Conclusion

Conclusions and Relevance: “In this open-label, non-randomized, uncontrolled study, a high rate of SVR12 was achieved in treatment-naive and treatment-experienced noncirrhotic patients with chronic HCV genotype 1 infection who received 12 weeks of treatment with the oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir.”

Source: Poordad F, et al. JAMA 2015;313:1728-35.

Treatment-Naïve and Treatment-Experienced

Daclatasvir-Asunaprevir-Beclabuvir in Genotype 1 Cirrhotics

UNITY-2 Study

Muir A, et al. JAMA 2015;313:1736-44.

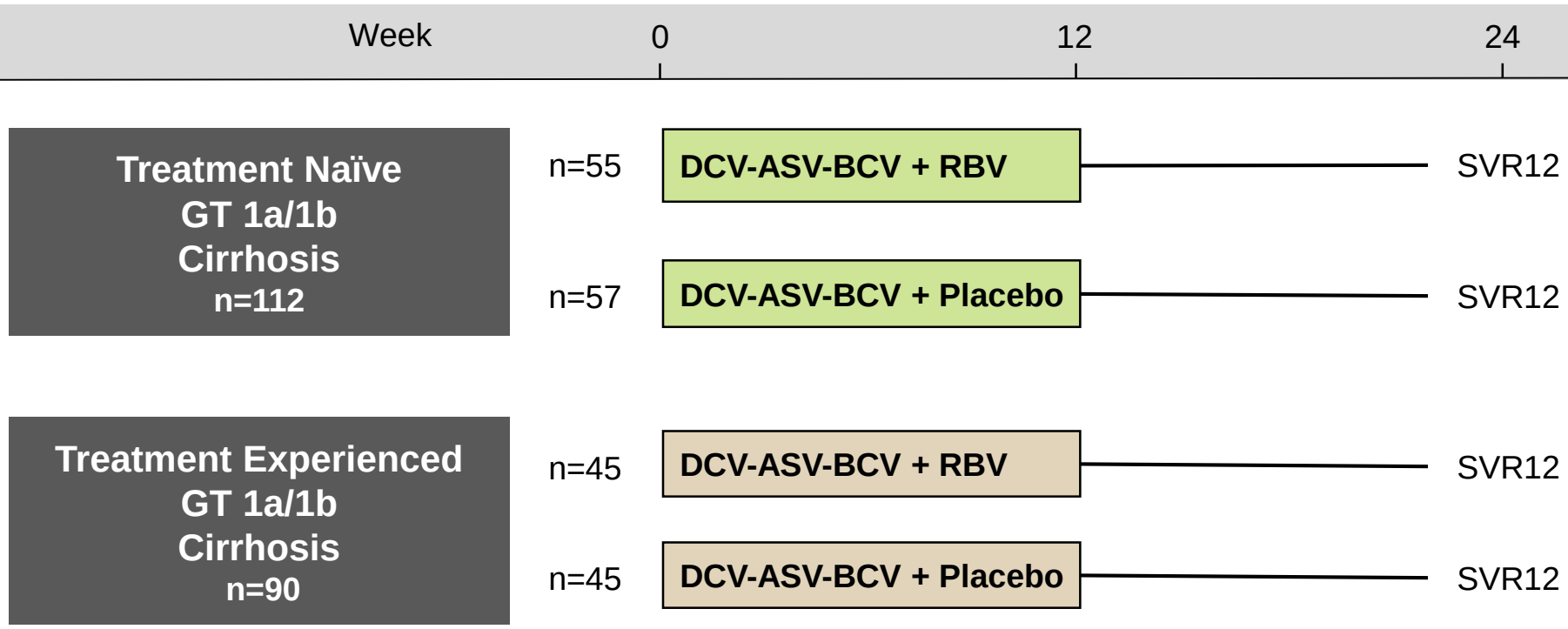
Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1 UNITY-2 Trial: Study Features

Daclatasvir-Asunaprevir-Beclabuvir Trial: Features

- **Design**: Multicenter, randomized, double-blind phase 3 trial of daclatasvir-asunaprevir-beclabuvir (fixed-dose combination) +/- ribavirin in treatment-naïve or experienced, chronic HCV GT 1 patients with compensated cirrhosis
- **Setting**: Multiple centers in the United States, Canada, Australia, France
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - Compensated cirrhosis (METAVIR F4 or equivalent by biopsy, *FibroScan* >14.6 kPa or *FibroTest*/*FibroSURE* ≥0.75 or APRI >2)
  - Platelets >50,000 cells/mm^3
  - Albumin > 3.5 g/dL and INR < 1.7
  - Treatment-naïve or treatment-experienced
  - HCV RNA ≥10,000 IU/ml
- **End-Points**: Primary = SVR12

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1
UNITY-2 Trial: Study Design



Drug Dosing

Daclatasvir (DCV)-Asunaprevir (ASV)-Beclabuvir (BCV) (30/200/75 mg): fixed dose combination BID

Ribavirin (RBV): weight-based and divided BID (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1
UNITY-2 Trial: Patient Characteristics

Characteristic	Treatment-Naive	
	DCV-ASV-BCV + RBV (n=55)	DCV-ASV-BCV (n=57)
Male	35 (64%)	39 (68%)
Median age, years (range)	59 (35-73)	58 (25-75)
Race White Black/African American Asian	 46 (84%) 6 (11%) 1 (2%)	 49 (86%) 6 (11%) 0
HCV RNA ≥800,000 IU/ml	41 (75%)	93 (90%)
HCV subtype 1A	39 (71%)	75 (73%)
IL28B non-CC genotype	37 (67%)	43 (75%)
Platelets x 10^3/µl ≥125 100-<125 50-<100 25-<50	 28 (51%) 10 (18%) 16 (29%) 1 (2%)	 35 (63%) 13 (23%) 8 (14%) 0

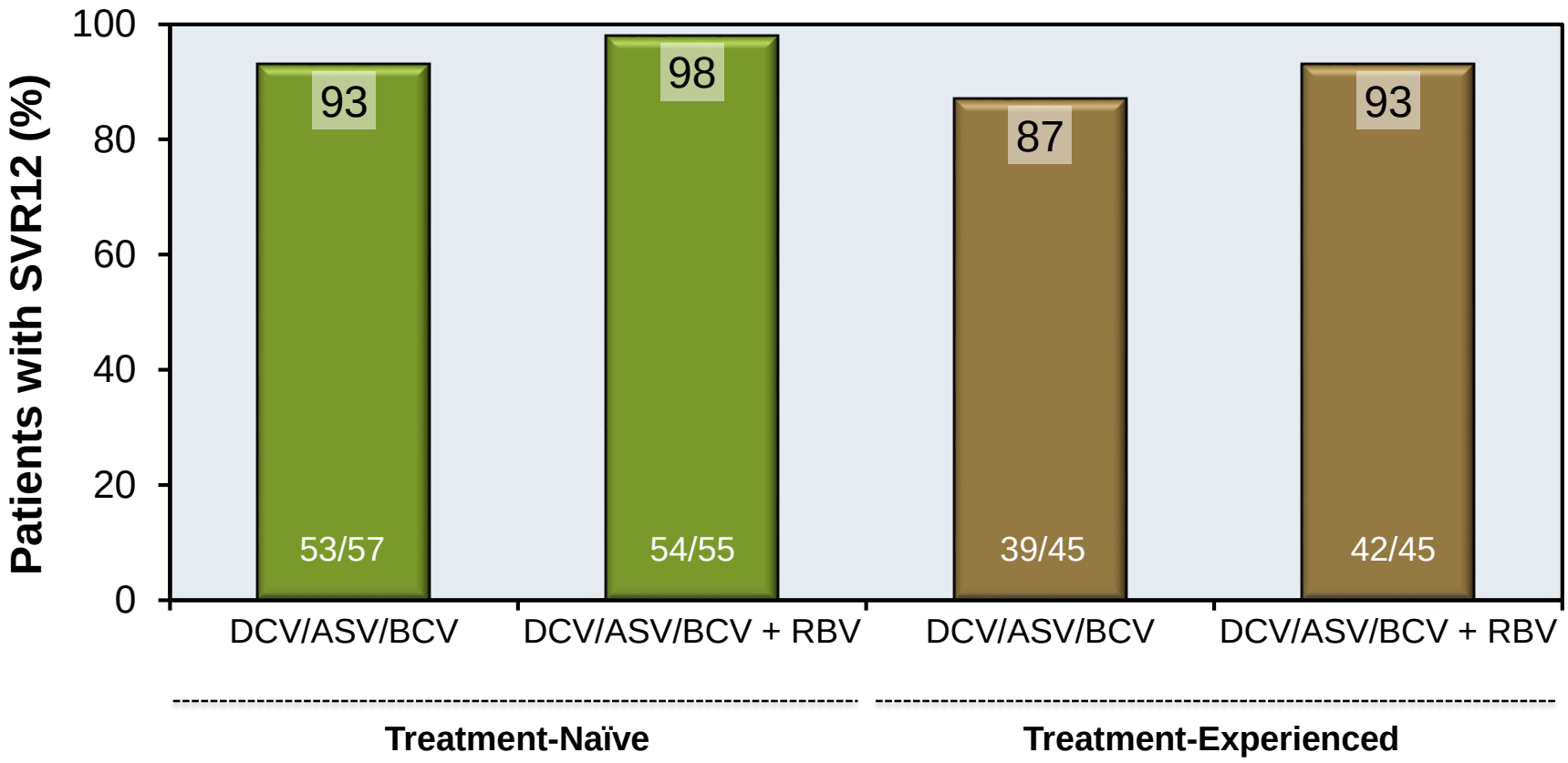
Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1
UNITY-2 Trial: Patient Characteristics

Characteristic	Treatment-Experienced	
	DCV-ASV-BCV + RBV (n=45)	DCV-ASV-BCV (n=45)
Male	27 (60%)	32 (71%)
Median age, years (range)	60 (48-73)	59 (19-76)
Race		
White	37 (82%)	41 (91%)
Black/African American	6 (13%)	2 (4%)
Asian	1 (2%)	2 (4%)
HCV RNA ≥800,000 IU/ml	41 (91%)	43 (96%)
HCV subtype 1A	35 (78%)	35 (78%)
IL28B non-CC genotype	35 (80%)	30 (67%)
Prior Treatment Outcome		
Relapse	8 (18%)	8 (18%)
Partial Response	2 (4%)	6 (13%)
Null Response	16 (36%)	19 (42%)
Interferon-intolerant	10 (22%)	6 (13%)

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1
UNITY-2 Trial: Results

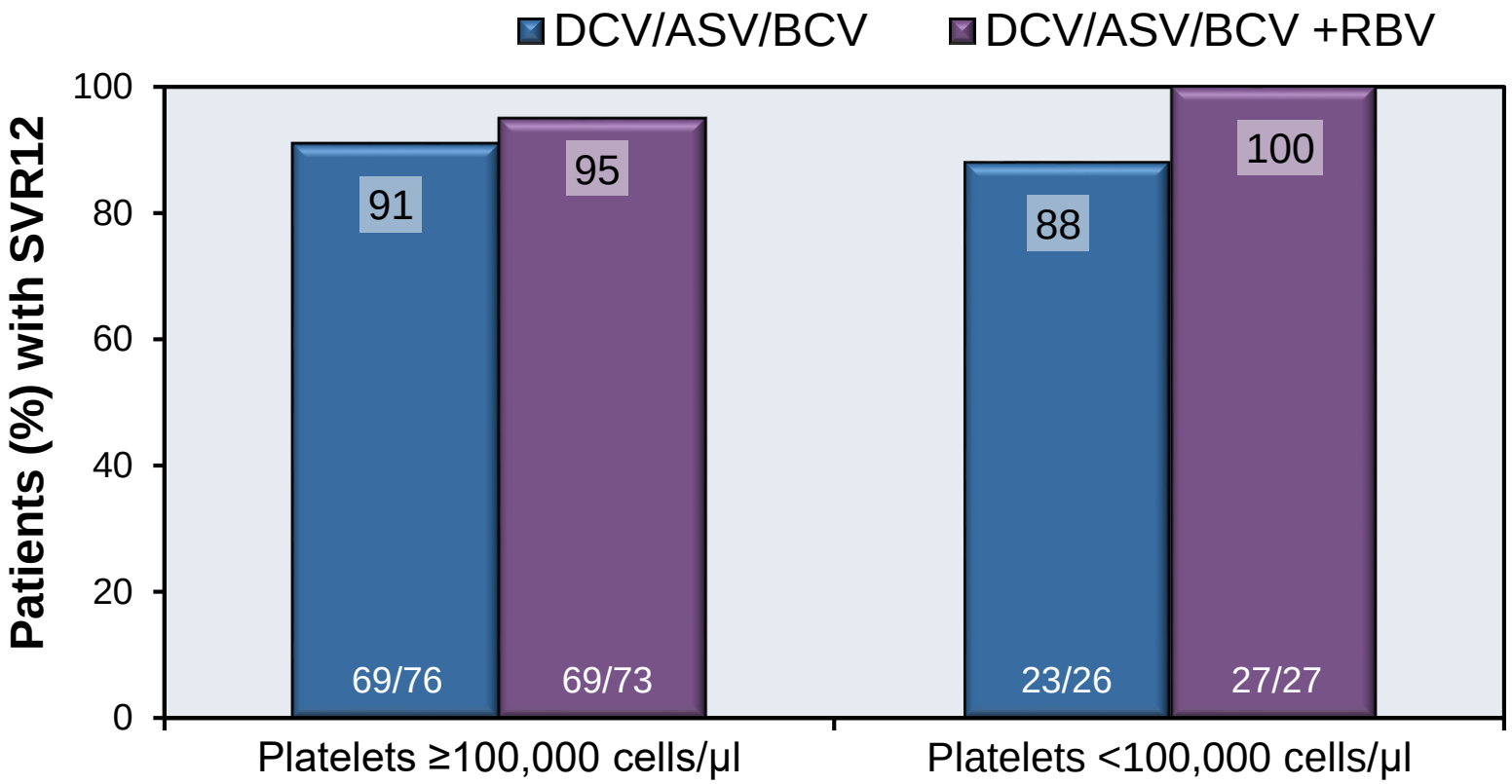


Abbreviations: DCV=daclatasvir; ASV=asunaprevir; BCV=beclabuvir; RBV=ribavirin

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1
UNITY-2 Trial: Results

UNITY-2: SVR12 by Regimen and Platelet Count



Abbreviations: DCV=daclatasvir; ASV=asunaprevir; BCV=beclabuvir; RBV=ribavirin

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1 UNITY-2 Trial: Adverse Events

Event (%)	DCV-ASV-BCV (n=102)	DCV-ASV-BCV + RBV (n=100)
Serious Adverse Events (AEs)	2	7
AEs leading to discontinuation of all meds	0	1
Adverse Events, ≥10% incidence		
Fatigue	12	28
Headache	17	23
Nausea	14	17
Diarrhea	13	9
Insomnia	6	15
Pruritus	6	15
Grade 3 or 4 Lab Abnormalities		
Hemoglobin < 9 g/dl	0	5
ALT >5 x ULN	3	1
Lipase, total >3 x ULN	5	1

Abbreviations: DCV=daclatasvir; ASV=asunaprevir; BCV=beclabuvir; RBV=ribavirin; ULN = upper limit of normal

Source: Muir A, et al. JAMA 2015;313:1736-44.

Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1 UNITY-2 Trial: Conclusion

Conclusions and Relevance: “In this open-label, uncontrolled study, patients with chronic HCV genotype 1 infection and cirrhosis who received a 12-week oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir, with or without ribavirin, achieved high rates of SVR12.”

Source: Muir A, et al. JAMA 2015;313:1736-44.

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Asunaprevir in Genotype 1b

HALLMARK-DUAL Study

Manns M, et al. Lancet. 2014;384:1597-605.

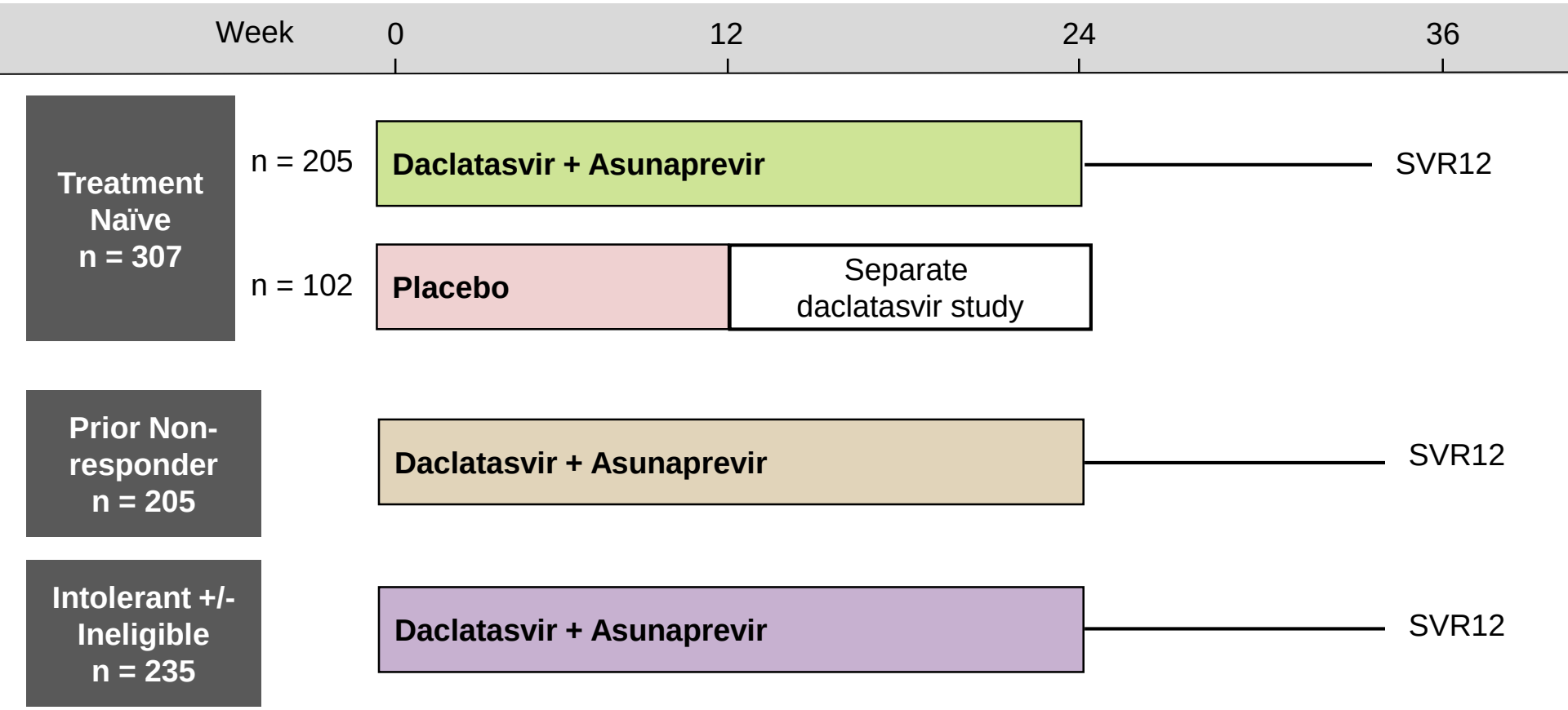
Daclatasvir + Asunaprevir for HCV GT 1b
HALLMARK-DUAL: Study Features

Daclatasvir + Sofosbuvir Trial: Features

- **Design**: Phase 3 open-label multi-cohort study of daclatasvir (DCV) plus asunaprevir in treatment-naïve or experienced, chronic HCV GT 1b
- **Setting**: 18 countries in North & South America, Europe and Asia
- **Entry Criteria**
  - Chronic HCV Genotype 1b
  - Treatment-naïve or treatment-experienced (prior null or partial responder to peginterferon + ribavirin)
  - Ineligible or intolerant (or both) to peginterferon + ribavirin
  - Compensated cirrhosis allowed
- **Patient Groups**
  - N = 307 treatment-naïve randomized to DCV + asunaprevir x 24 weeks versus placebo (latter then enrolled in separate DCV study)
  - N = 205 treatment-experienced: DCV + asunaprevir x 24 weeks
  - N = 235 Peg/RBV intolerant +/- ineligible: DCV + asunaprevir x 24 weeks
- **End-Points**: Primary = SVR12

Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir for HCV GT 1B
HALLMARK-DUAL: Study Design



Drug Dosing
Daclatasvir: 60 mg once daily
Asunaprevir: 100 mg twice daily

Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir for HCV GT 1B
HALLMARK-DUAL: Patient Characteristics

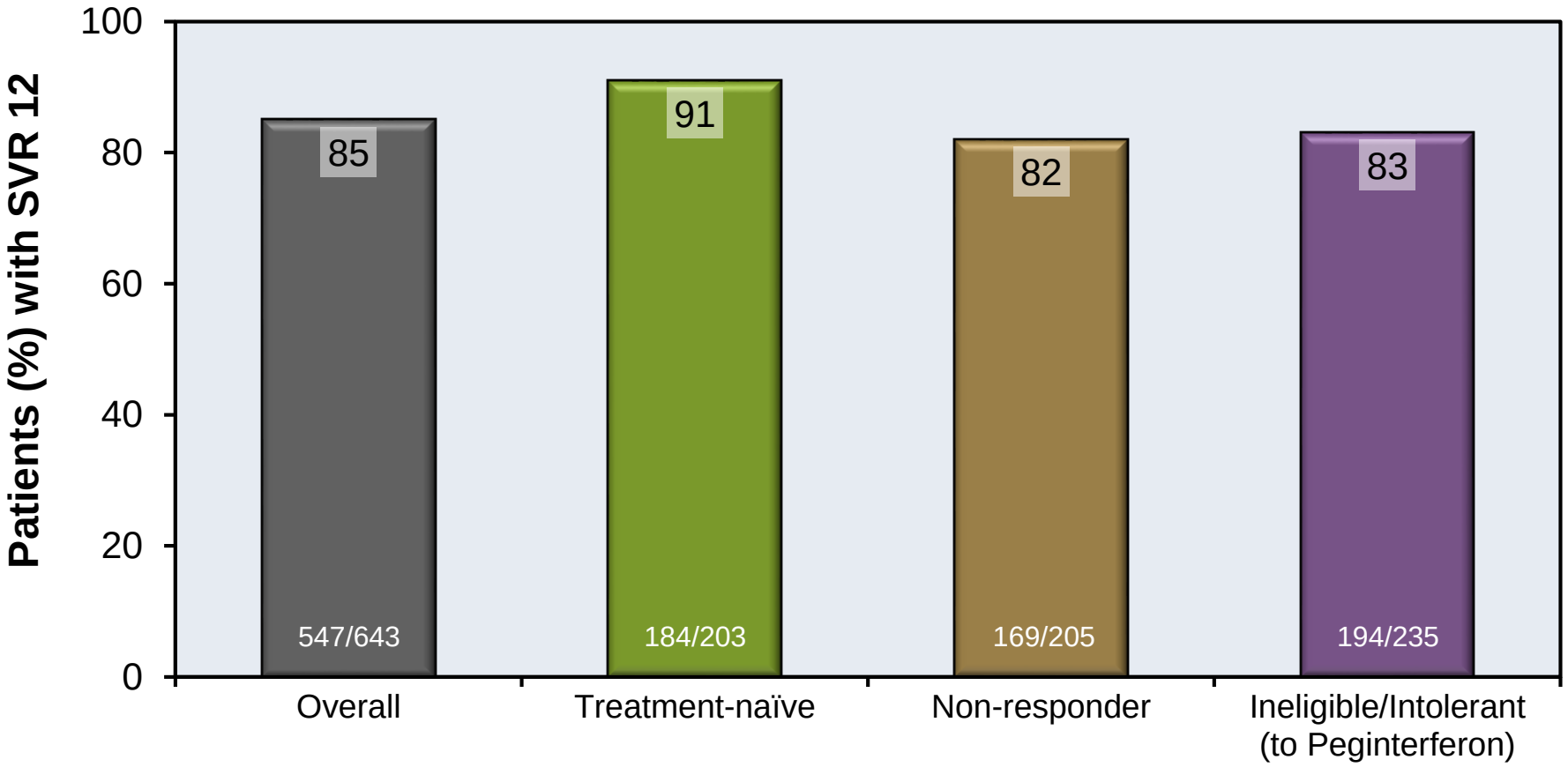
Characteristic	Treatment-naïve on DCV + ASV (n=205)	Treatment-naïve on Placebo (n=102)	Prior Non-responder (n=205)	Intolerant/ Ineligible (n=235)
Age (years)	55 (20-79)	54 (22-83)	58 (23-77)	60 (24-77)
Men	101 (49%)	54 (53%)	111 (54%)	98 (42%)
Race White Black Asian	 135 (66%) 14 (7%) 52 (25%)	 59 (58%) 8 (8%) 45 (22%)	 148 (72%) 10 (5%) 45 (22%)	 169 (72%) 10 (4%) 56 (24%)
HCV RNA ≥800,000 IU/ml	152 (74%)	76 (75%)	178 (87%)	187 (80%)
Cirrhosis	33 (16%)	16 (16%)	63 (31%)	111 (47%)
Prior response to P/R Null Partial	N/A	N/A	 119 (58%) 84 (41%)	N/A
Ineligible/intolerant reason Depression Anemia/neutropenia Advanced F3 or F4[a]	N/A	N/A	N/A	 71 (30%) 87 (37%) 77 (33%)

DCV=daclatasvir; ASV=asunaprevir. [a]Compensated (Child A) if cirrhotic but with thrombocytopenia.

Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir in Genotype 1b
HALLMARK-DUAL Study

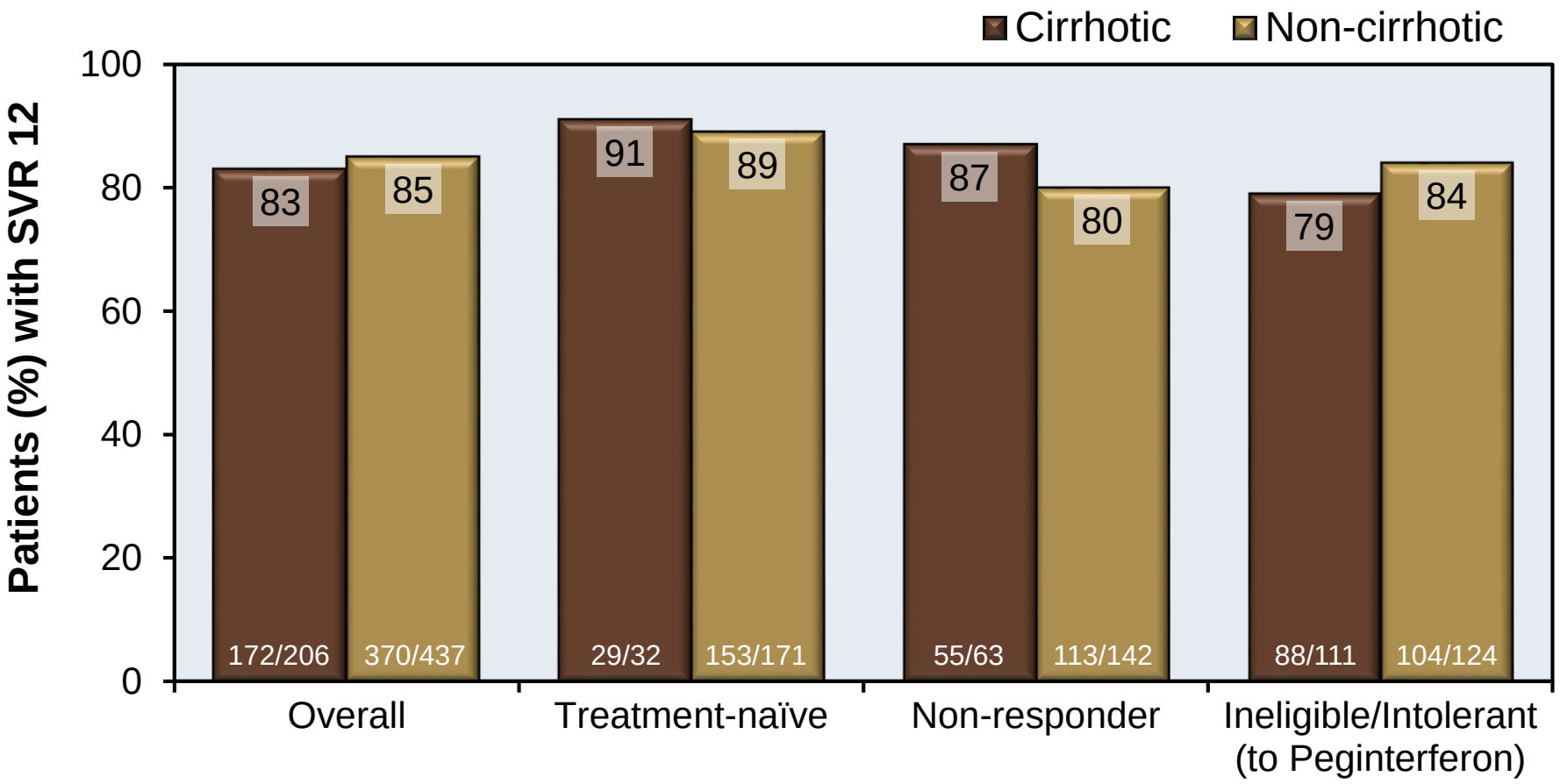
HALLMARK-DUAL: SVR12, by Treatment Experience



Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir in Genotype 1b
HALLMARK-DUAL Study

HALLMARK-DUAL: SVR12, by Cirrhosis Status



Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir for HCV GT 1B
HALLMARK-DUAL: Adverse Events

Adverse Effects	Treatment-naïve on DCV + ASV (n=205)	Treatment-naïve on Placebo (n=102)	Prior Non-responder (n=205)	Intolerant/Ineligible (n=235)
Any adverse event	176 (86%)	74 (73%)	167 (81%)	204 (87%)
Serious adverse events	12 (6%)	1 (1%)	11 (5%)	16 (7%)
Adverse events leading to discontinuation	6 (3%)	0	2 (1%)	2 (1%)
Adverse events in ≥10% in any cohort				
Headache	50 (24%)	17 (17%)	50 (24%)	59 (25%)
Fatigue	43 (21%)	18 (18%)	45 (22%)	52 (22%)
Diarrhea	24 (12%)	10 (10%)	28 (14%)	51 (22%)
Nausea	25 (12%)	12 (12%)	22 (11%)	28 (12%)
Asthenia	4 (2%)	1 (1%)	12 (6%)	25 (11%)
Grade 3-4 lab events				
ALT 5.1-10 x ULN	1 (<1%)	2 (2%)	3 (1%)	3 (1%)
ALT >10 x ULN	6 (3%)	0	1 (<1%)	1 (<1%)
AST 5.1-10 x ULN	5 (2%)	1 (1%)	1 (<1%)	2 (1%)
AST >10 x ULN	2 (1%)	0	1 (<1%)	1 (<1%)

ULN, upper limit of normal

Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir + Asunaprevir for HCV GT 1b
HALLMARK-DUAL: Conclusions

Interpretation: “Daclatasvir plus asunaprevir provided high sustained virological response rates in treatment-naive, non-responder, and ineligible, intolerant, or ineligible and intolerant patients, and was well tolerated in patients with HCV genotype 1b infection. These results support the use of daclatasvir plus asunaprevir as an all-oral, interferon-free and ribavirin-free treatment option for patients with HCV genotype 1b infection, including those with cirrhosis.”

Source: Manns M, et al. Lancet. 2014;384:1597-605.

Daclatasvir in HCV-HIV Coinfection

Hepatitis
web study

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir in HCV GT 1-4 and HIV Coinfection

ALLY-2 Study

Wyles DL, et al. N Engl J Med. 2015;373:714-25.

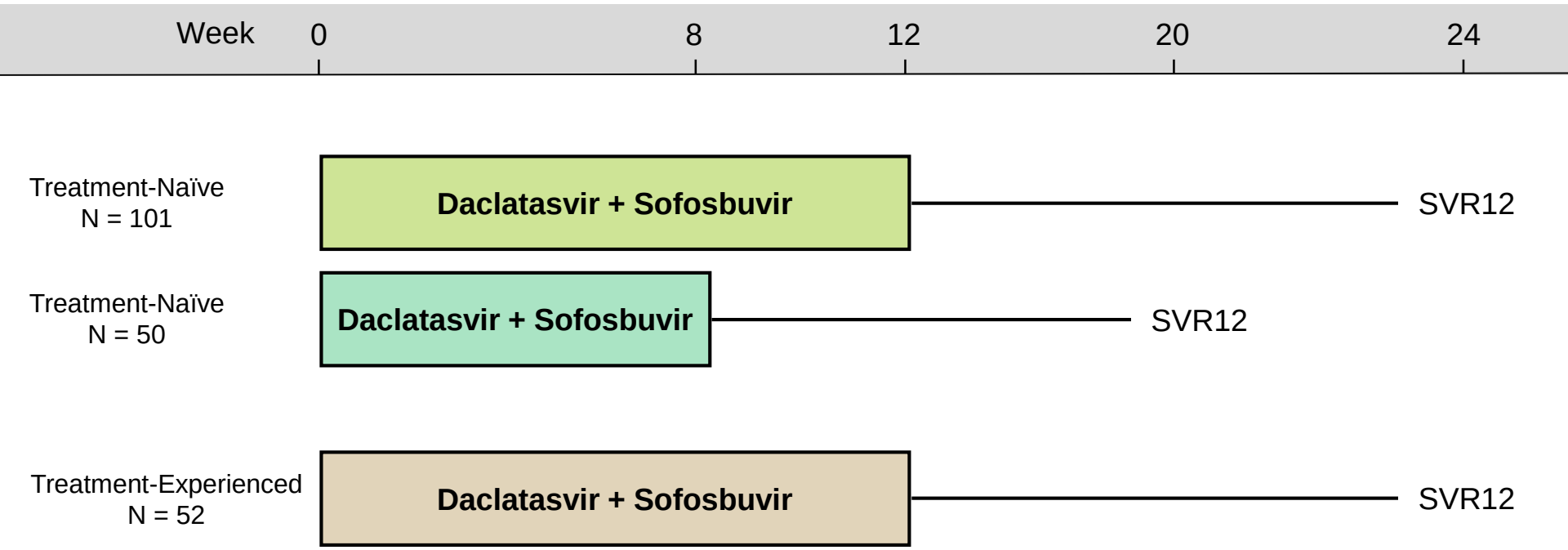
Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Study Features

ALLY-2: Features

- **Design**: Phase 3, open-label study of daclatasvir (DCV) plus sofosbuvir (SOF) in treatment-naïve or experienced, chronic HCV GT 1-4 and HIV coinfection
- **Setting**: Multiple centers in the United States
- **Entry Criteria**
  - N = 395 patients enrolled
  - Chronic HCV Genotype 1 through 4
  - Treatment-naïve or treatment experienced
  - Noncirrhotic or compensated cirrhosis (less than 50%)
  - Stable ARV with HIV RNA < 50 copies/ml at screening and <200 copies/ml for ≥8 weeks; and CD4 count > 100 cells/mm^3
  - ARVs allowed: tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, darunavir-ritonavir, atazanavir-ritonavir, lopinavir-ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc
- **End-Points**: Primary = SVR12

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Design



Drug Dosing

Daclatasvir: 60 mg once daily; with efavirenz and nevirapine the dose was increased to 90 mg once daily and with ritonavir-boosted protease inhibitors the dose was decreased to 30 mg once daily

Sofosbuvir: 400 mg once daily

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection ALLY-2 Trial: Patient Characteristics

Characteristic	Treatment-Naïve 12-Week Group (n=101)	Treatment-Naïve 8-Week Group (n=50)	Previously Treated 12-Week Group (n=52)
Male, n (%)	92 (91%)	42 (84%)	43 (83%)
Median age, years (range)	52 (24-71)	51 (28-75)	57 (43-66)
Race White Black Asian/other	 66 (65%) 30 (30%) 5 (5%)	 28 (56%) 19 (38%) 3 (6%)	 31 (60%) 20 (38%) 1 (2%)
HCV genotype 1A 1B 2 3 4	 71 (70%) 12 (12%) 11 (11%) 6 (6%) 1 (1%)	 35 (70%) 6 (12%) 6 (12%) 3 (6%) 0	 33 (63%) 11 (21%) 2 (4%) 4 (8%) 2 (4%)
Cirrhosis	9 (9%)	5 (10%)	15 (29%)
Median HCV RNA $\log_{10}$ (IU/mL)(range)	6.7 (3.3-7.6)	6.4 (4.2-7.5)	6.7 (3.9-7.9)

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

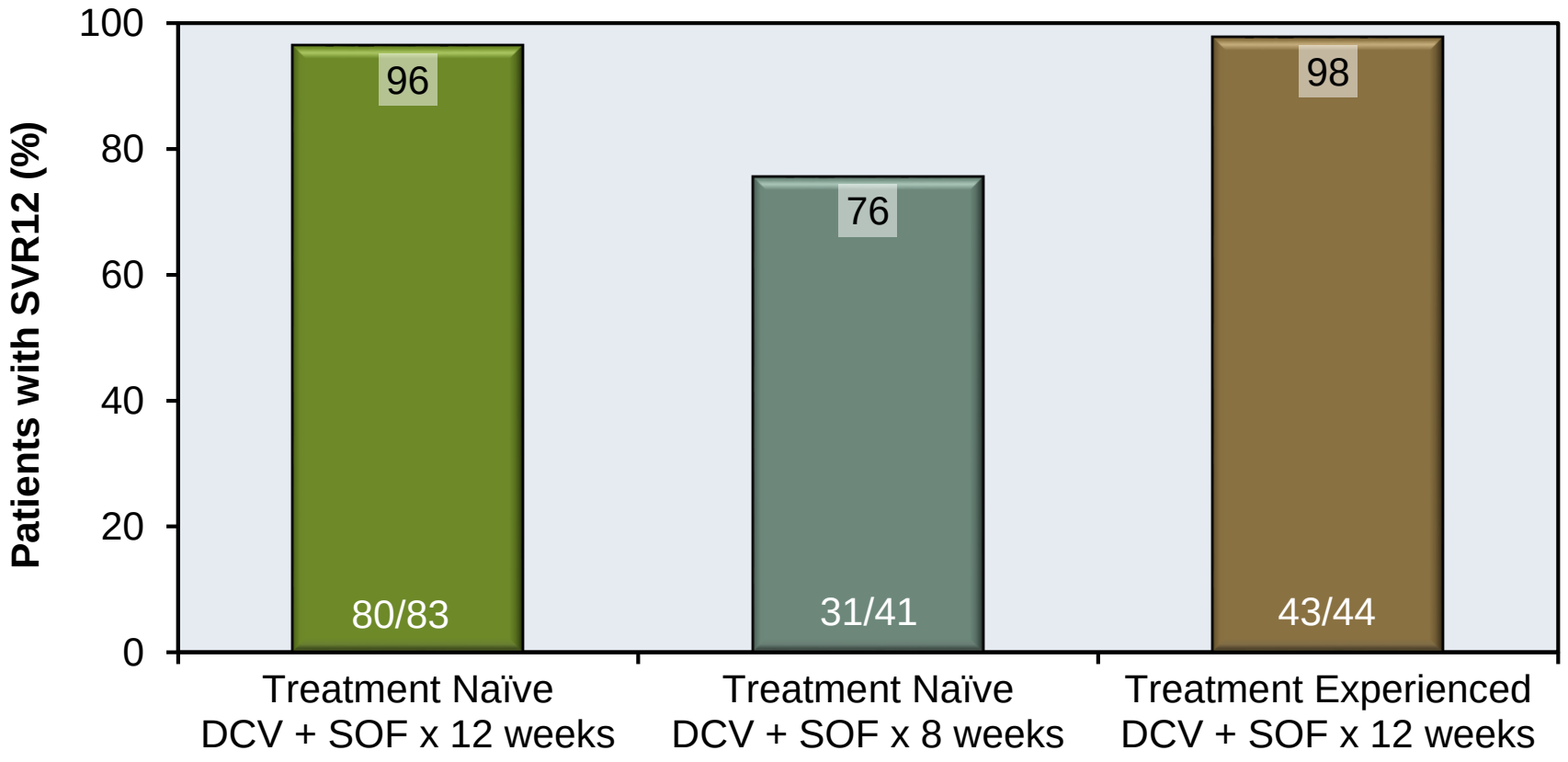
Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: HIV Characteristics

Characteristic	Treatment-Naïve 12-Week Group (n=101)	Treatment-Naïve 8-Week Group (n=50)	Previously Treated 12-Week Group (n=52)
Median CD4 count (range)— cells/mm^3	520 (122-1147)	575 (157-1430)	636 (262-1470)
HIV-1 RNA <50 copies/ml	94/100 (94%)	45/48 (94%)	47/49 (96%)
Antiretroviral treatment, %	Total 99%	Total 96%	Total 98%
Darunavir-ritonavir	19%	44%	22%
Atazanavir-ritonavir	19%	10%	24%
Lopinavir-ritonavir	9%	6%	0
Efavirenz	18%	17%	16%
Nevirapine	5%	2%	6%
Rilpivirine	5%	2%	2%
Raltegravir	22%	17%	20%
Dolutegravir	3%	2%	8%
Nucleoside RTI only	0	0	4%

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 1

SVR12, Genotype 1

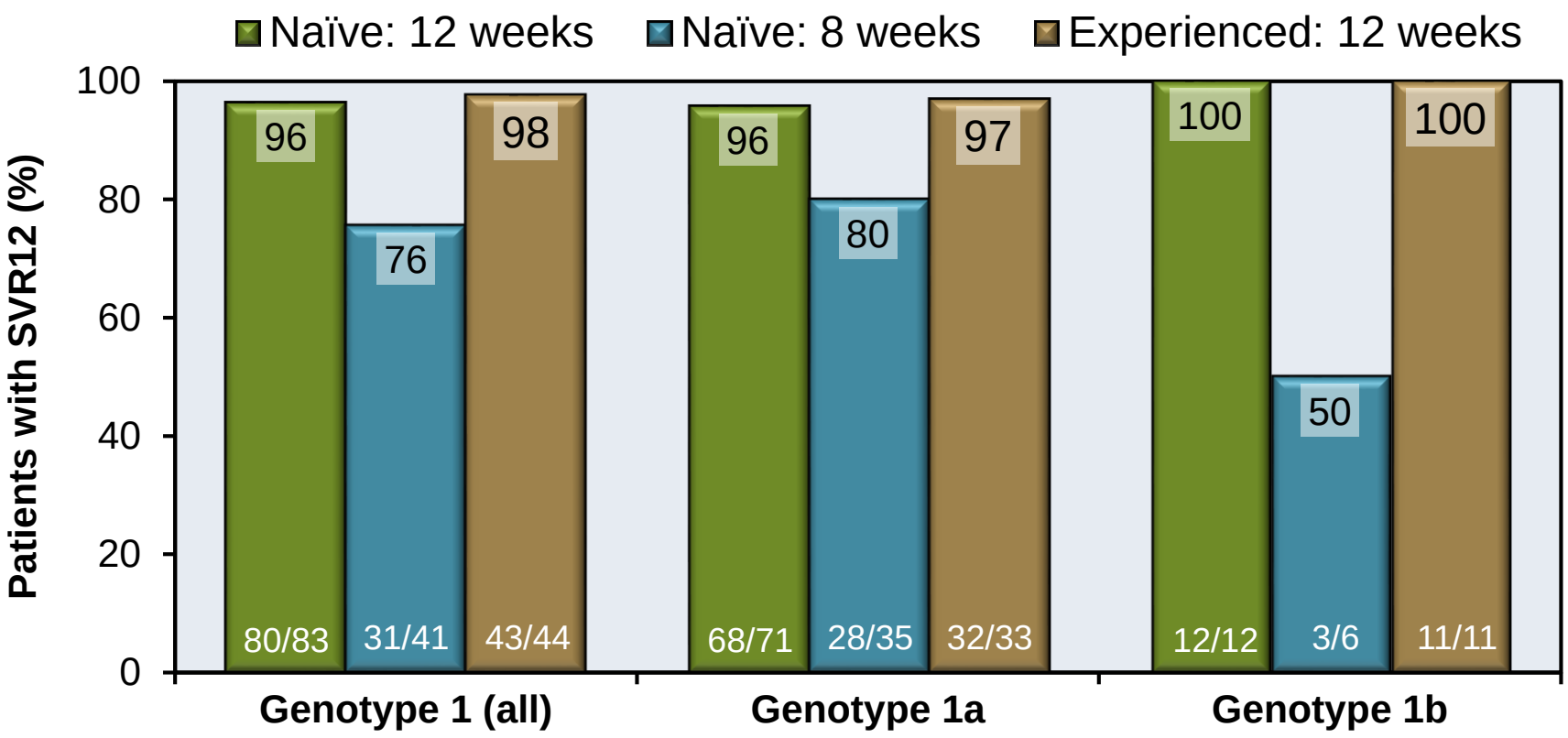


Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results

SVR12, Genotype 1 and subtypes

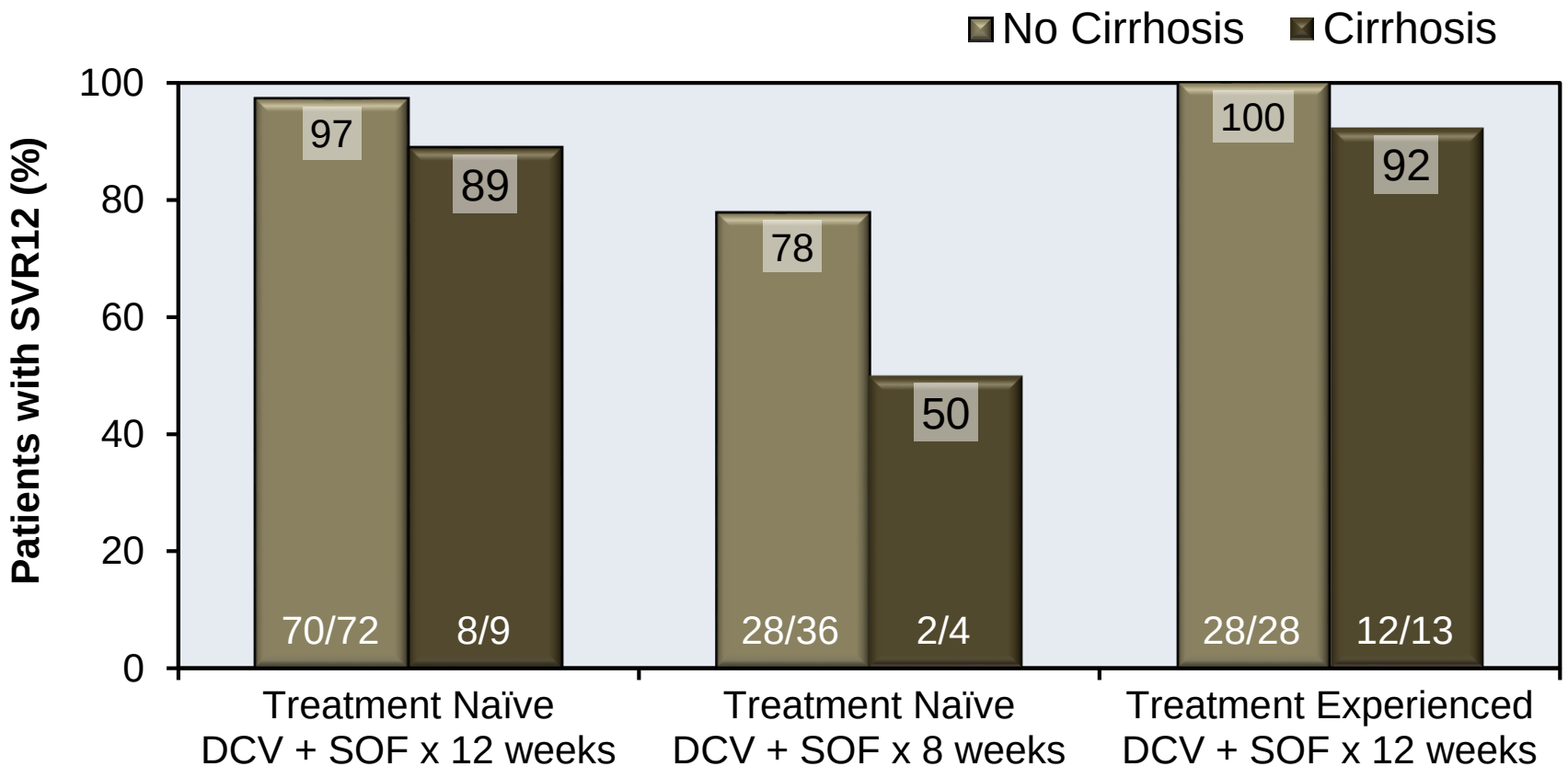


n=11 had missing or inconclusive findings for cirrhosis & not included in denominators

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 1

SVR12, Genotype 1, by Liver Status



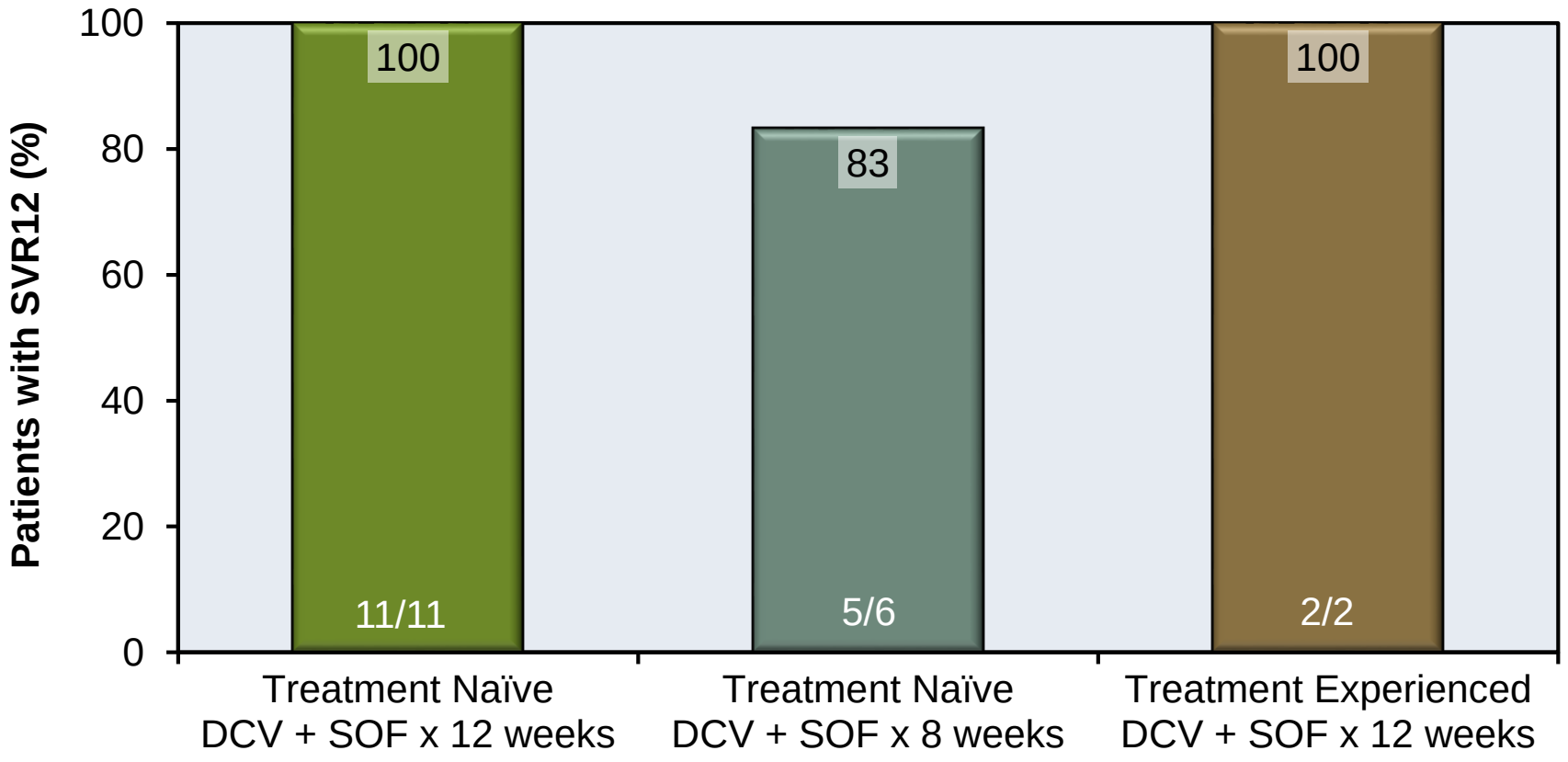
Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Hepatitis web study

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 2

SVR12, Genotype 2

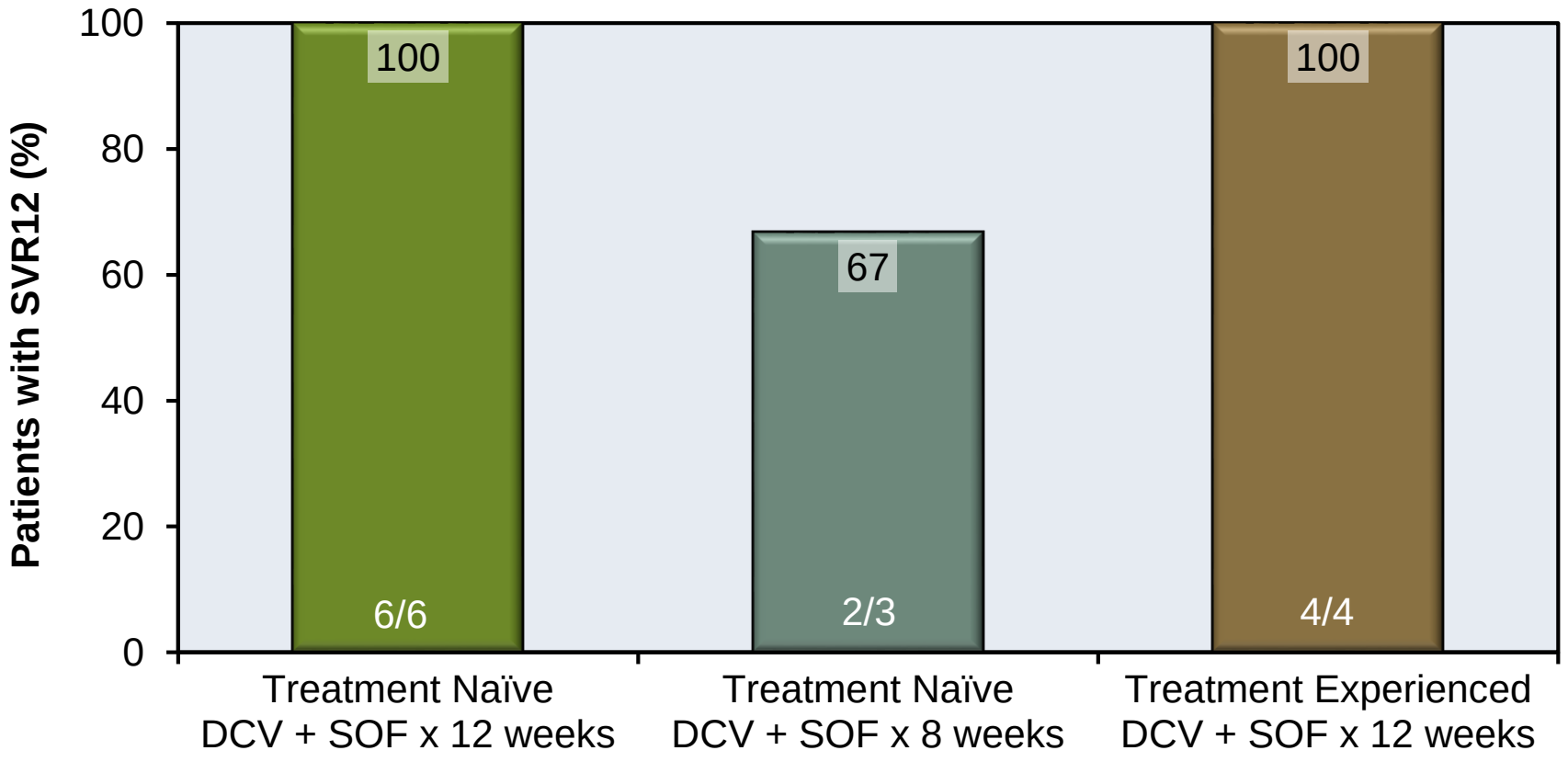


Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 3

SVR12, Genotype 3

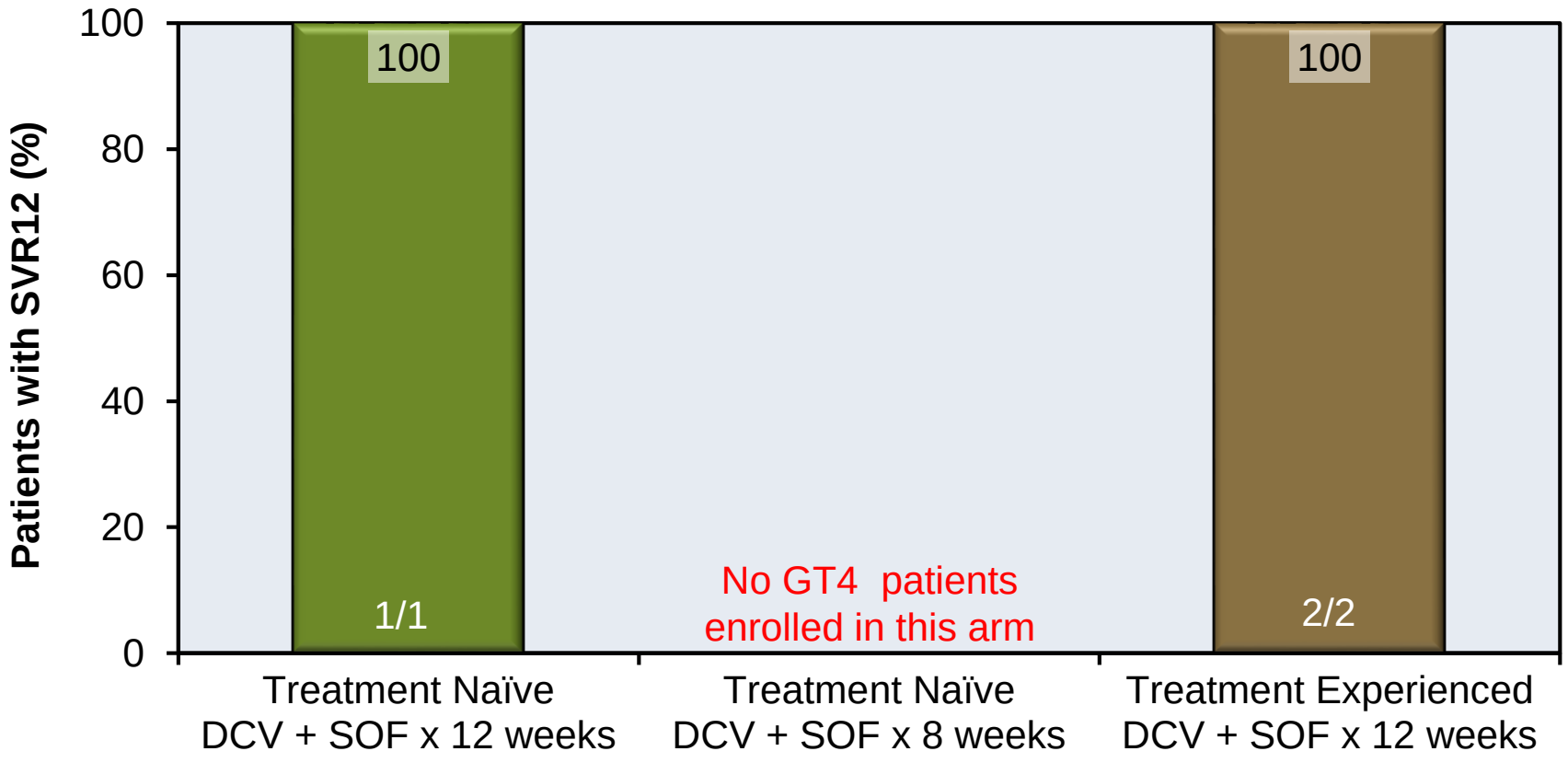


Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Results for Genotype 4

SVR12, Genotype 4



Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection ALLY-2 Trial: Conclusion

Conclusion: “Among previously untreated HIV–HCV coinfected patients receiving daclatasvir plus sofosbuvir for HCV infection, the rate of sustained virologic response across all genotypes was 97.0% after 12 weeks of treatment and 76.0% after 8 weeks.”

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

Daclatasvir in Patients Pre and Post Liver Transplant

Hepatitis
web study

Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir + Ribavirin in HCV with Advanced Cirrhosis or Post-Liver Transplant

ALLY-1 Study

Poordad F, et al. Hepatology. 2016;63:1493-505.

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant
ALLY-1: Results

ALLY-1: Features

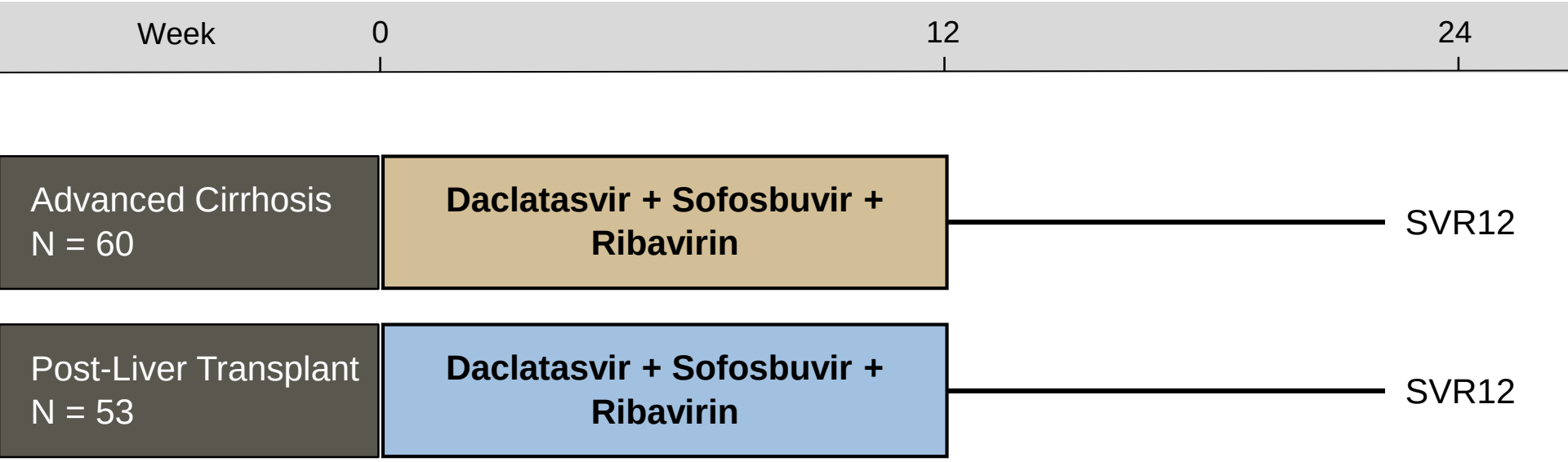
- **Design**: **Design**: Multicenter, prospective, open-label, phase 3 study of daclatasvir plus sofosbuvir plus ribavirin in treatment-naïve and treatment-experienced patients with advanced cirrhosis or post-liver transplant HCV recurrence.
- **Setting**: Five centers in United States
- **Entry Criteria**
  - Treatment-naïve or treatment-experienced
  - Chronic HCV genotypes 1-6
  - HCV RNA >10,000 IU/ml
  - Cirrhosis (compensated and decompensated) allowed
  - Post-liver transplant: received transplant ≥3 months prior to screening
- **Outcome Measure**: Primary = SVR12

Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant

ALLY-1: Results

ALLY-1: Study Design



Drug Dosing
Daclatasvir: 60 mg once daily
Sofosbuvir: 400 mg once daily
Ribavirin: 600 mg daily, adjusted to 1000 mg/day based on hemoglobin levels and renal function

Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant

ALLY-1: Patient Characteristics

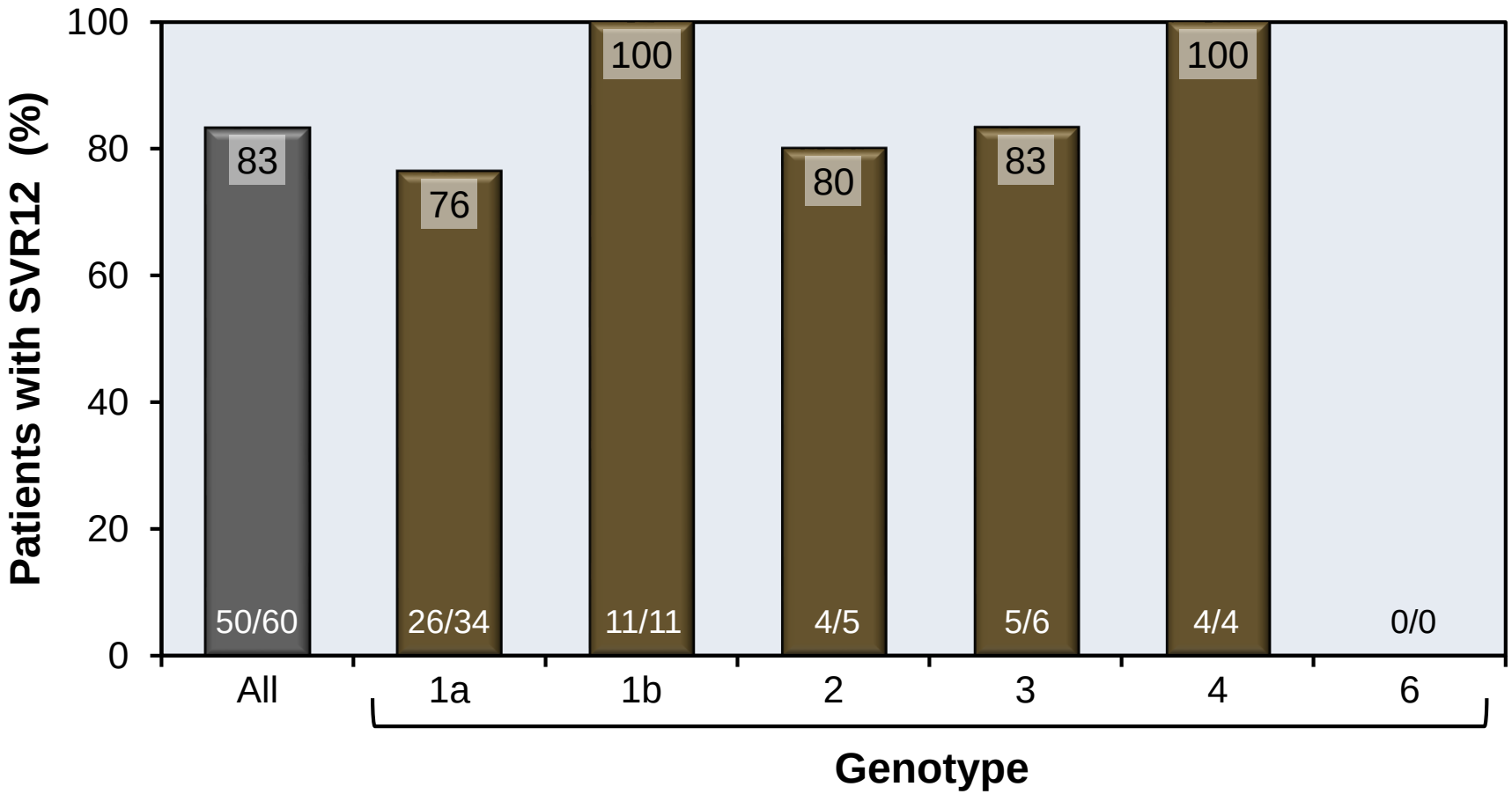
Characteristic	Advanced Cirrhosis (n=60)	Post-Liver Transplant (n=53)
Male, n (%)	38 (63%)	38 (72%)
Median age, years (range)	58 (19-75)	59 (22-82)
Race		
White	57 (95%)	51 (96%)
Black/African American	3 (5%)	1 (2%)
Asian	0 (0%)	1 (2%)
HCV genotype		
1a	34 (57%)	31 (58%)
1b	11 (18%)	10 (19%)
2	5 (8%)	0 (0%)
3	6 (10%)	11 (21%)
4	4 (7%)	0 (0%)
6	0	1 (2%)
Mean HCV RNA $\log_{10}$ (IU/mL)	6.01	6.61

Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant

ALLY-1: Results for Advanced Cirrhosis Cohort

ALLY-1: SVR12 Results for Advanced Cirrhosis Cohort by Genotype



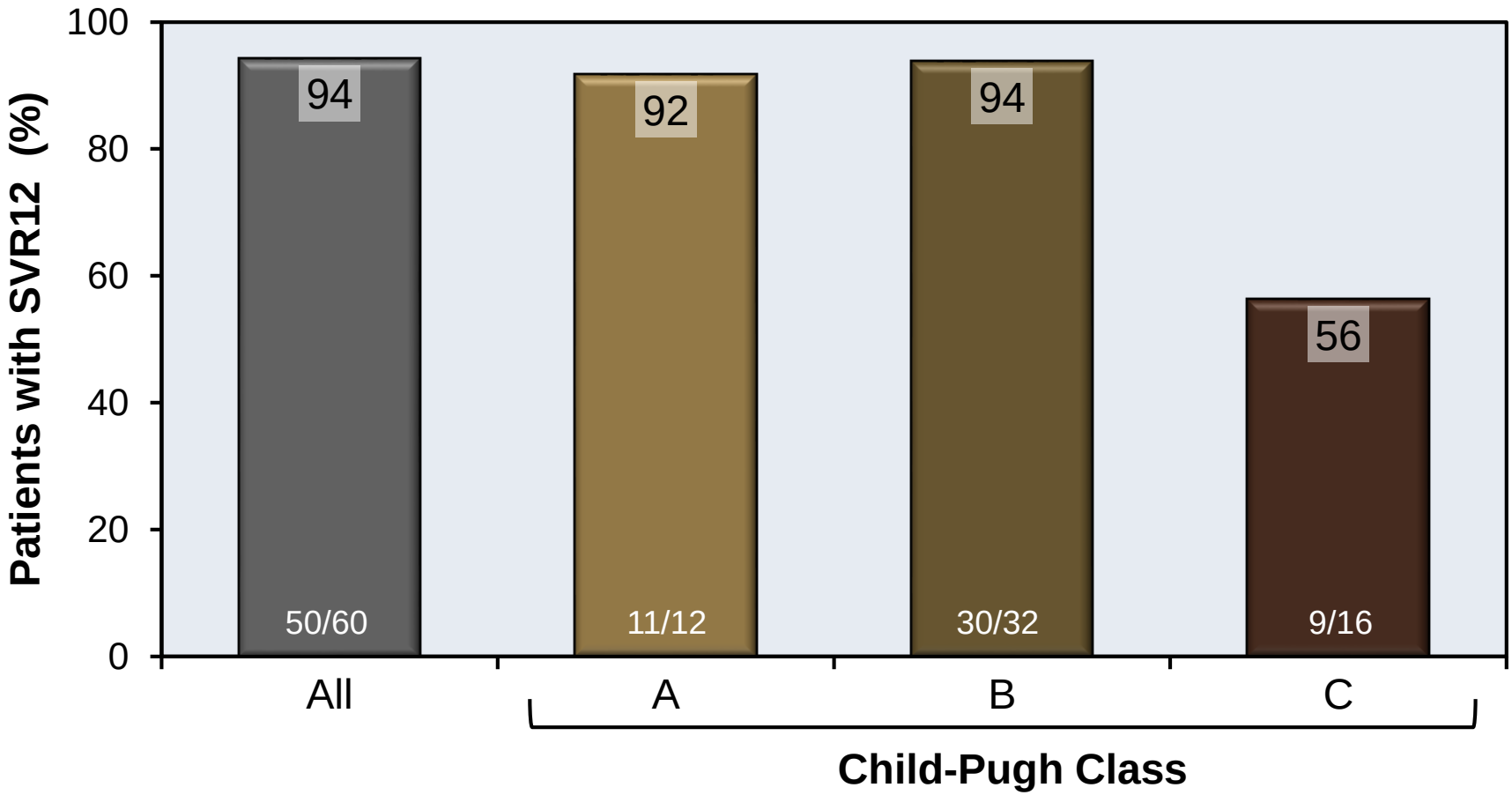
Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

Hepatitis web study

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant

ALLY-1: Results for Advanced Cirrhosis Cohort

ALLY-1: SVR12 Results for Advanced Cirrhosis Cohort by Child-Pugh Class

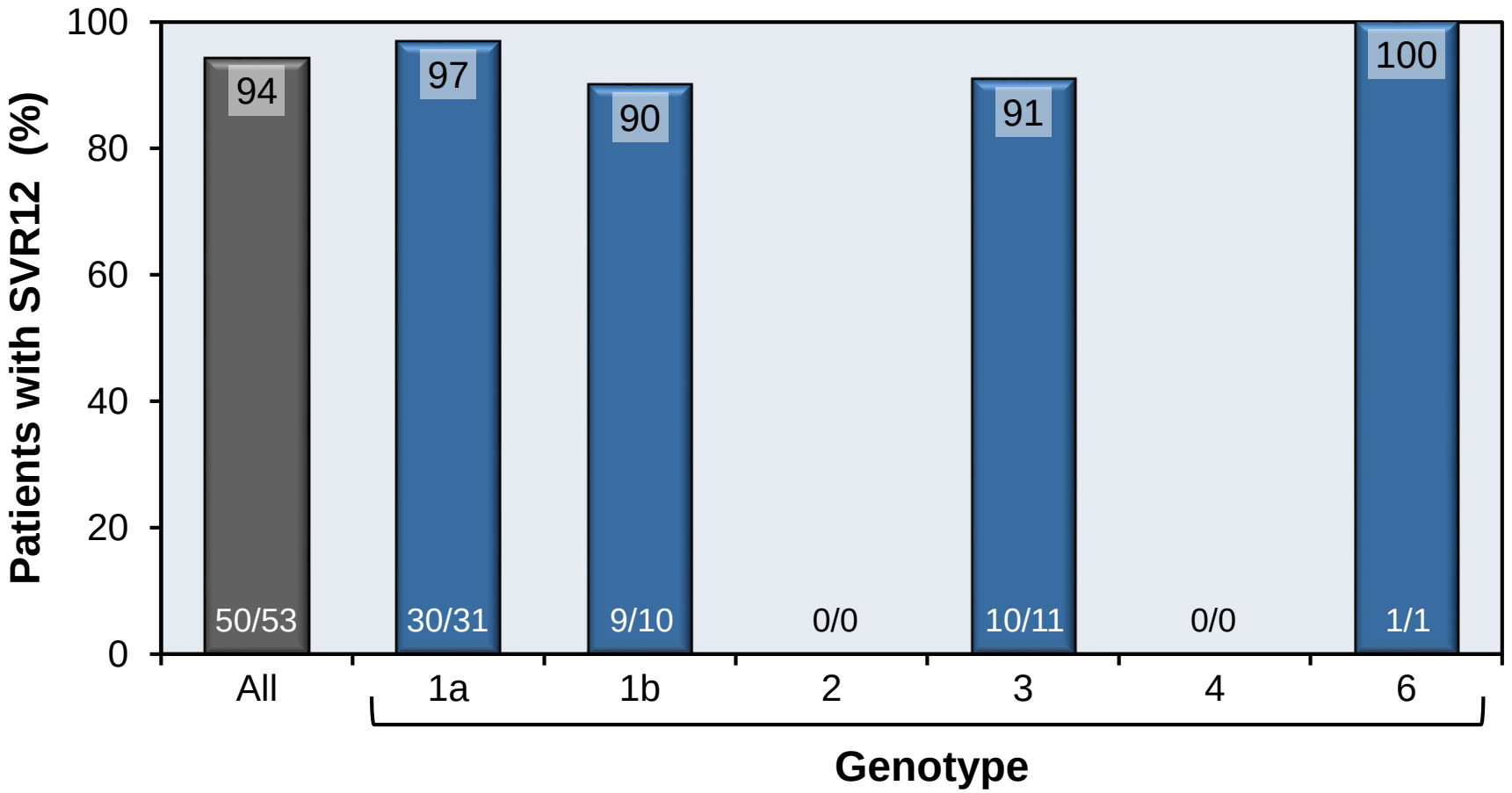


Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant

ALLY-1: Results for Post-Liver Transplant Cohort

ALLY-1: SVR12 Results for Post-Liver Transplant Cohort by Genotype



Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

Hepatitis web study

DCV + SOF + RBV in Advanced Cirrhosis and Post-Liver Transplant
ALLY-1: Conclusion

Conclusion: “The pan-genotypic combination of daclatasvir, sofosbuvir, and ribavirin was safe and well tolerated. High SVR rates across multiple HCV genotypes were achieved by patients with post-liver transplant recurrence or advanced cirrhosis.”

Source: Poordad F, et al. Hepatology. 2016;63:1493-505.

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

http://depts.washington.edu/hepstudy/

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Hepatitis
web study