HEPATITIS WEB STUDY HEPATITIS C ONLINE

Daclatasvir (*Daklinza*)

Prepared by: H. Nina Kim, MD MSc and David Spach, MD
Last Updated: July 27, 2015

Hepatitis web study

DACLATASVIR (*DAKLINZA*)

Background Information

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Daclatasvir (*Daklinza*)

- **Approval Status**: Approved by United States FDA July 24, 2015
- **Indications and Usage**
  - Indicated with sofosbuvir for the treatment of chronic HCV genotype 3 in adults
- **Treatment Course**
  - For GT3: Daclatasvir 60 mg plus Sofosbuvir 400 mg once daily x 12 weeks
  - Both medications taken with or without food
- **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

Source: *Daklinza* Prescribing Information. Bristol Myers Squibb

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 (*Hypericuum 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 3 Trial in Treatment-Naïve and Experienced GT 3
  - **ALLY-3:** Daclatasvir + sofosbuvir
- 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

Daclatasvir: Summary of Key Studies

- Phase 3 Trial in Treatment-Experienced GT 1 or 4
  - **HALLMARK-QUAD:** Daclatasvir + asunaprevir + PEG/RBV
- Phase 3 Trial in Treatment-Naïve GT 4
  - **COMMAND-4:** Daclatasvir + PEG/RBV vs Placebo + PEG/RBV
- Phase 3 Trial in Treatment-Naïve and Experienced GT 1-4 and HIV
  - **ALLY-2:** Daclatasvir + sofosbuvir

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

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Treatment-Naïve and Treatment-Experienced

Daclatasvir + Sofosbuvir in Genotype 3
ALLY-3 Study

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

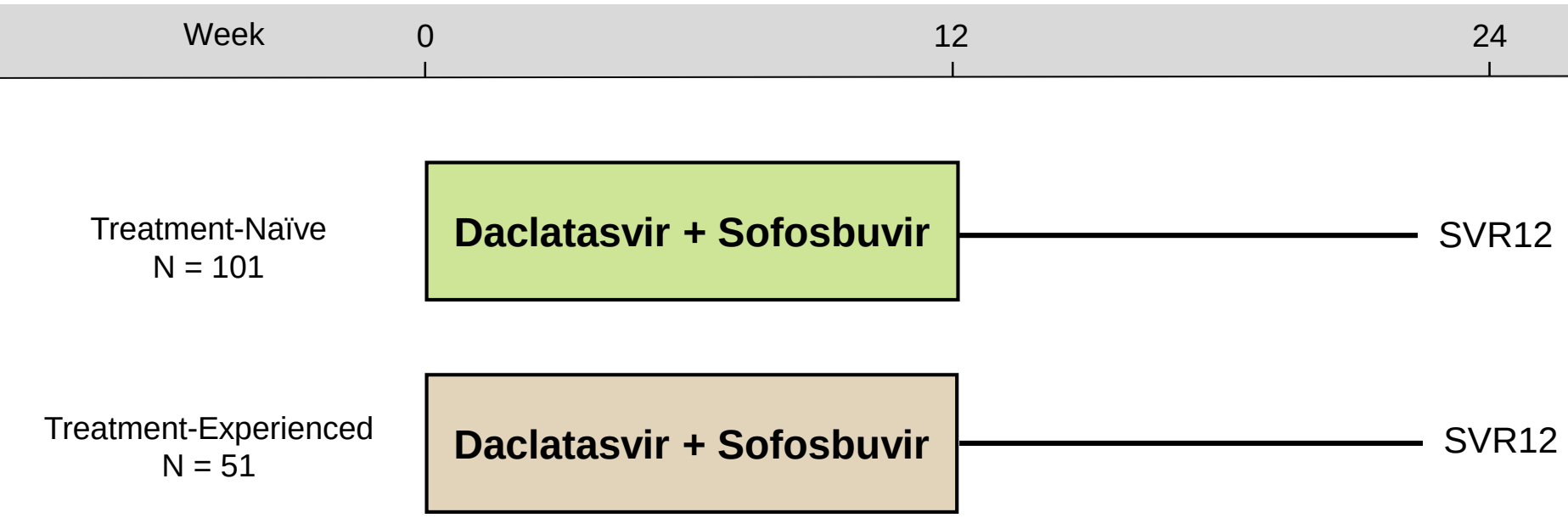
Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Study Features

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 patients received 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

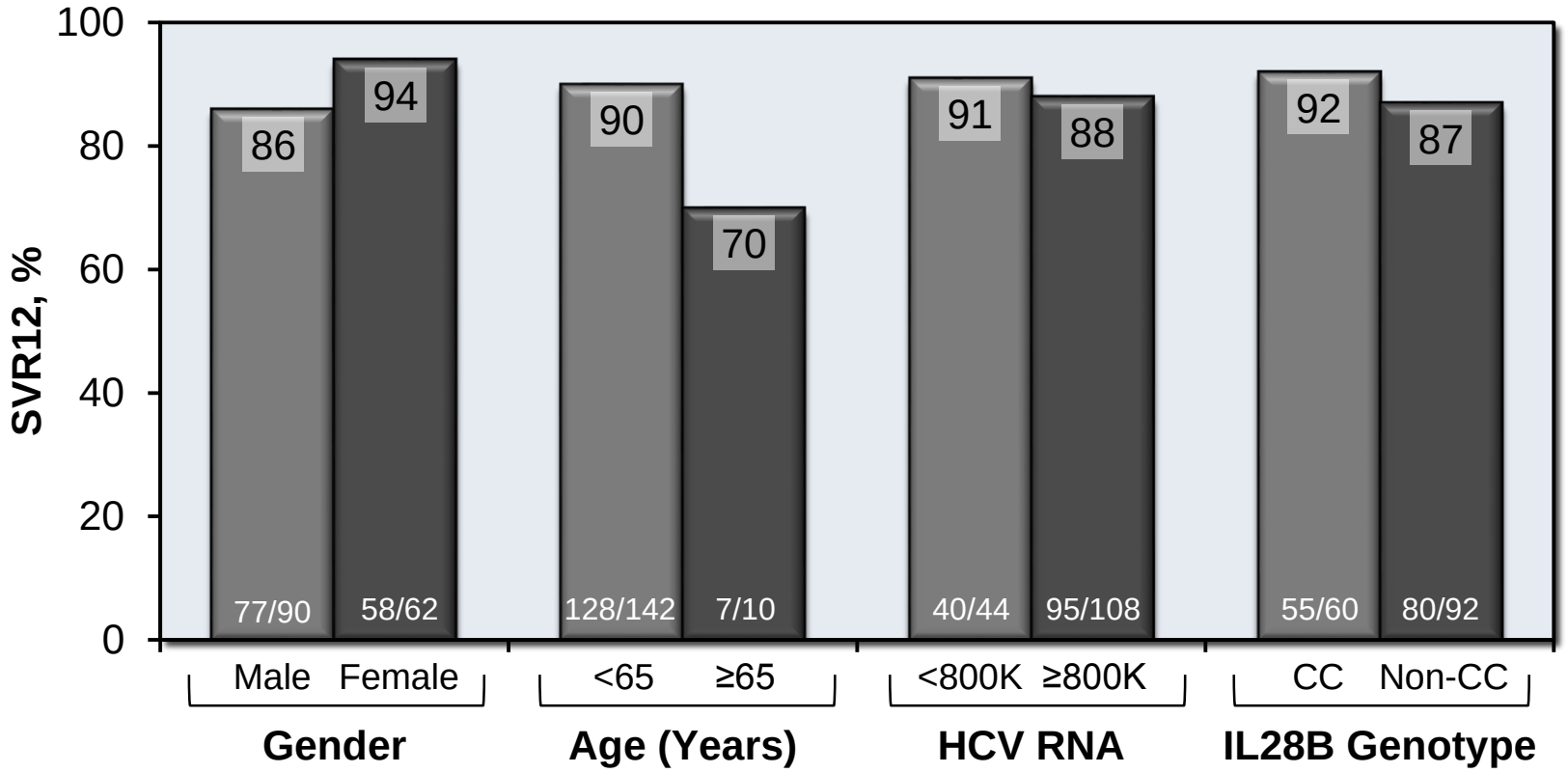
Characteristic	Treatment-Naïve (n=101)	Treatment-Experienced (n=51)
Male	58 (57%)	32 (63%)
Median age, years (range)	53 (24-67)	58 (40-73)
Race		
White	92 (91%)	45 (88%)
Black	4 (4%)	2 (4%)
Asian	5 (5%)	2 (4%)
HCV RNA ≥800,000 IU/ml	70 (69%)	38 (75%)
Cirrhosis	19 (19%)	13 (25%)
IL28B non-CC genotype	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 tx (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.

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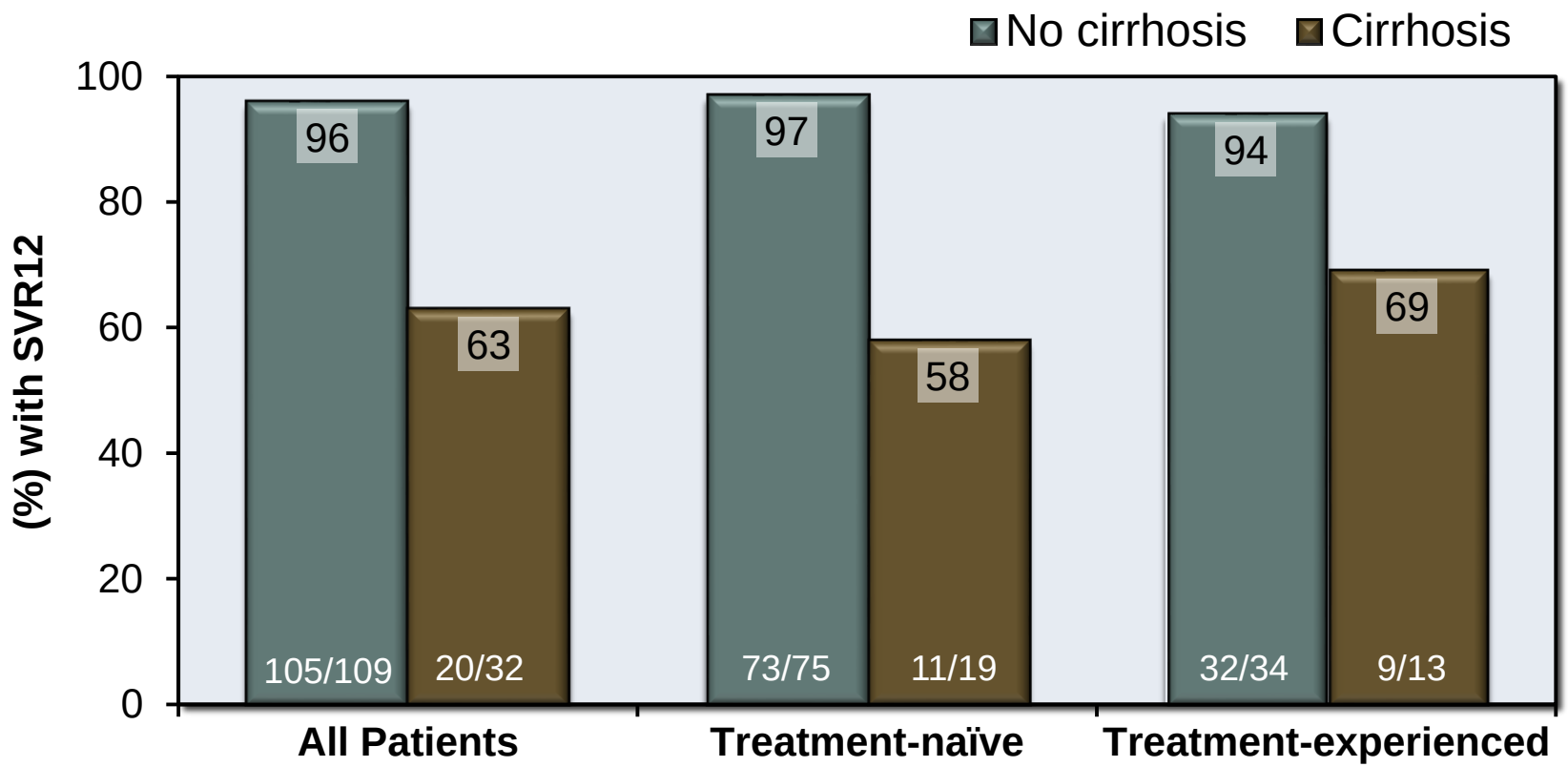
Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Results

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 +/- Ribavirin in Genotype 1-3
AI444040 Trial

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

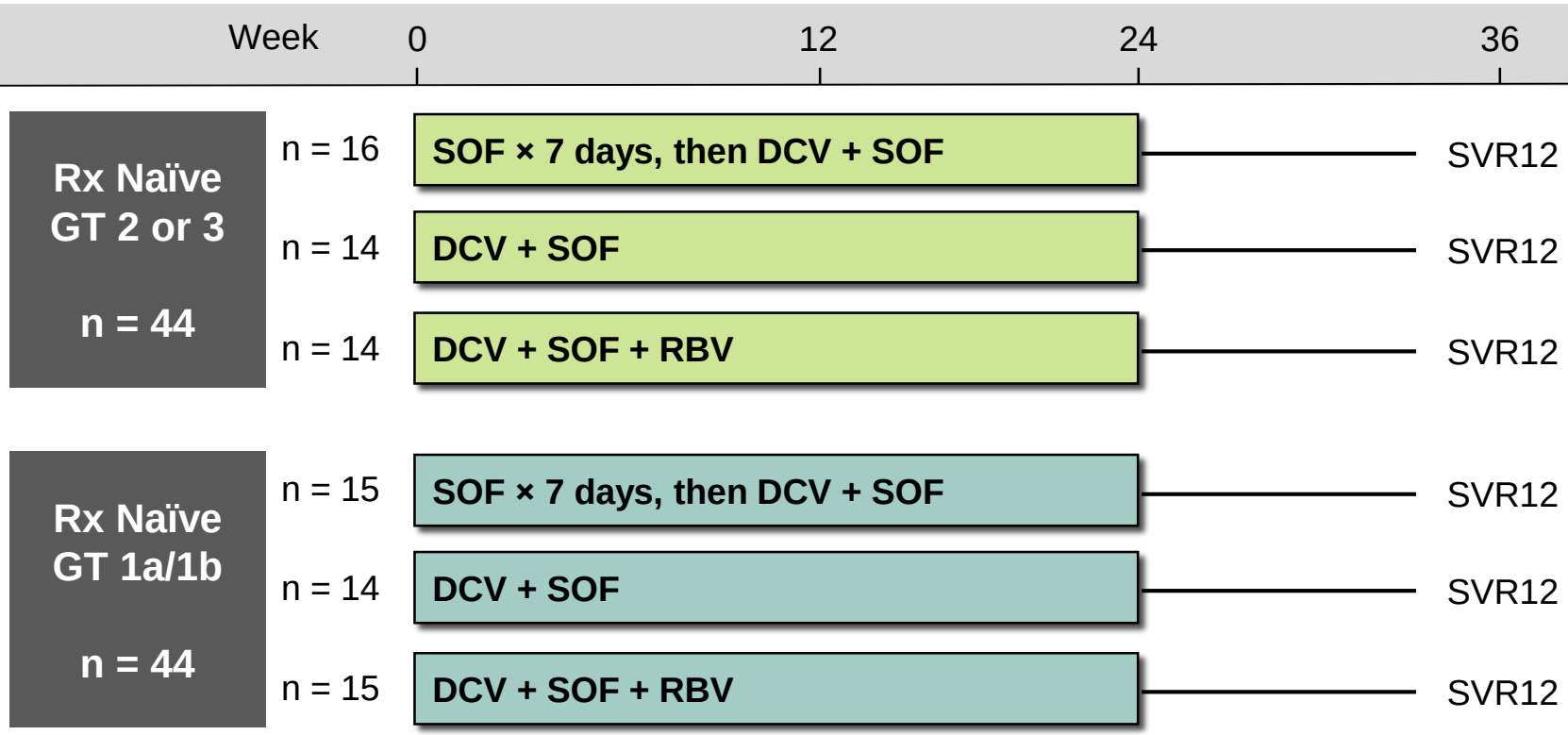
Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Trial: Study Features

Daclatasvir + Sofosbuvir Trial: Features

- **Design**: Randomized, open label, phase 2a, using declatasvir + sofosbuvir +/- 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
  - 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
Trial Design: Treatment-Naïve 24 Week Rx



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

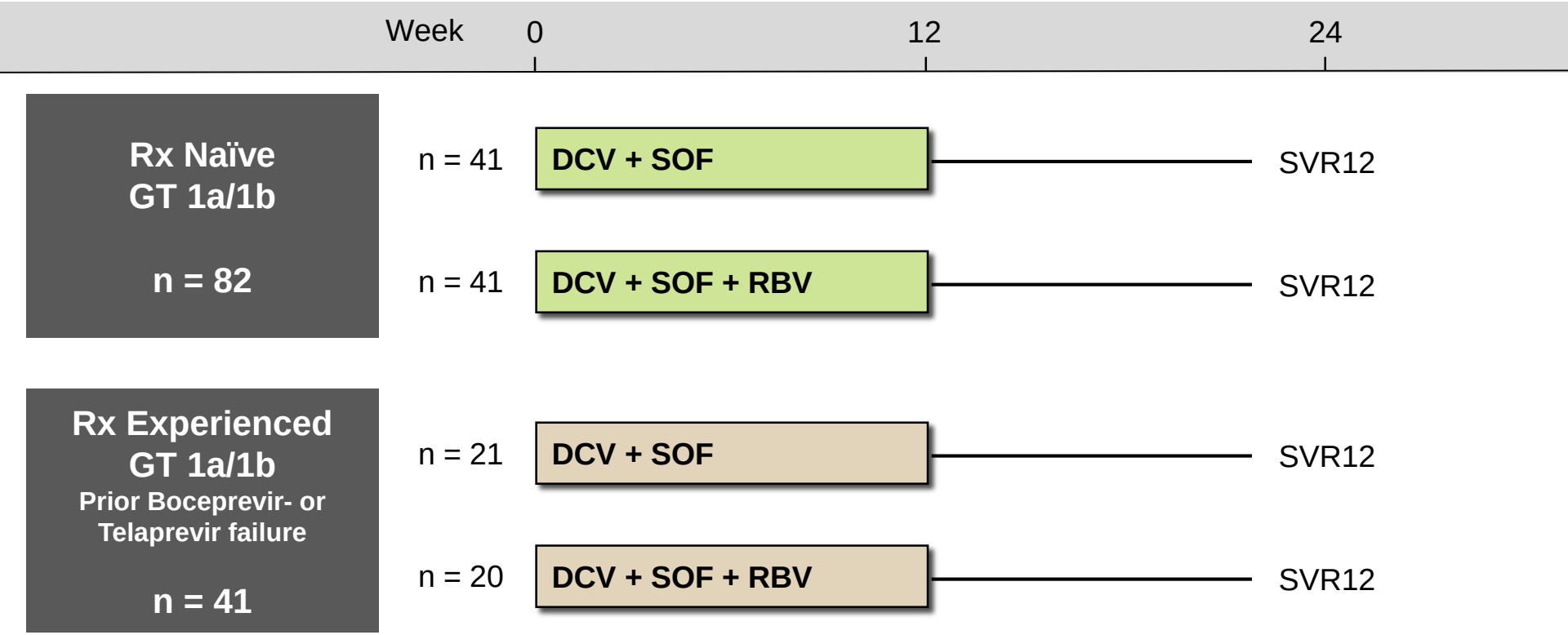
Sofosbuvir (SOF): 400 mg once daily

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
Design: GT1 Treatment-Naïve & Experienced 12 Week Rx



Drug Dosing

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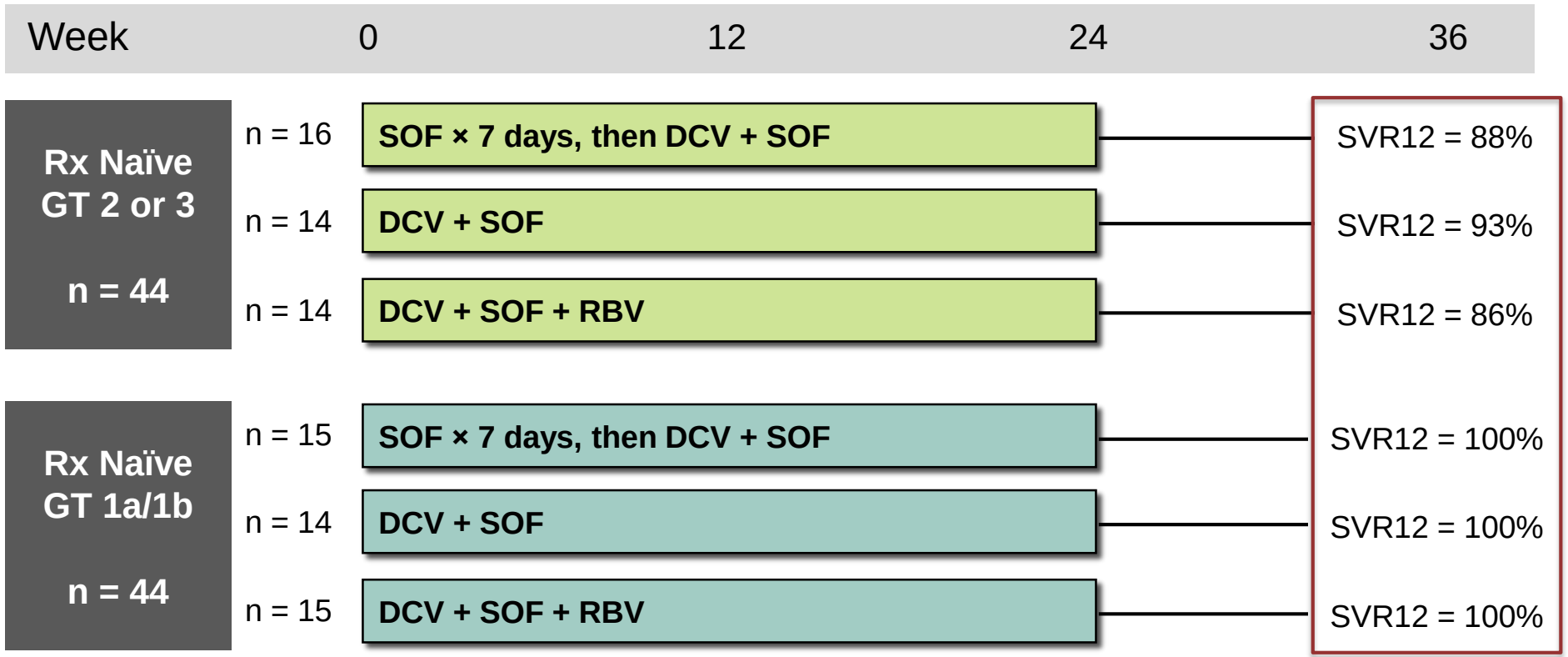
Sofosbuvir (SOF): 400 mg once daily

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



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

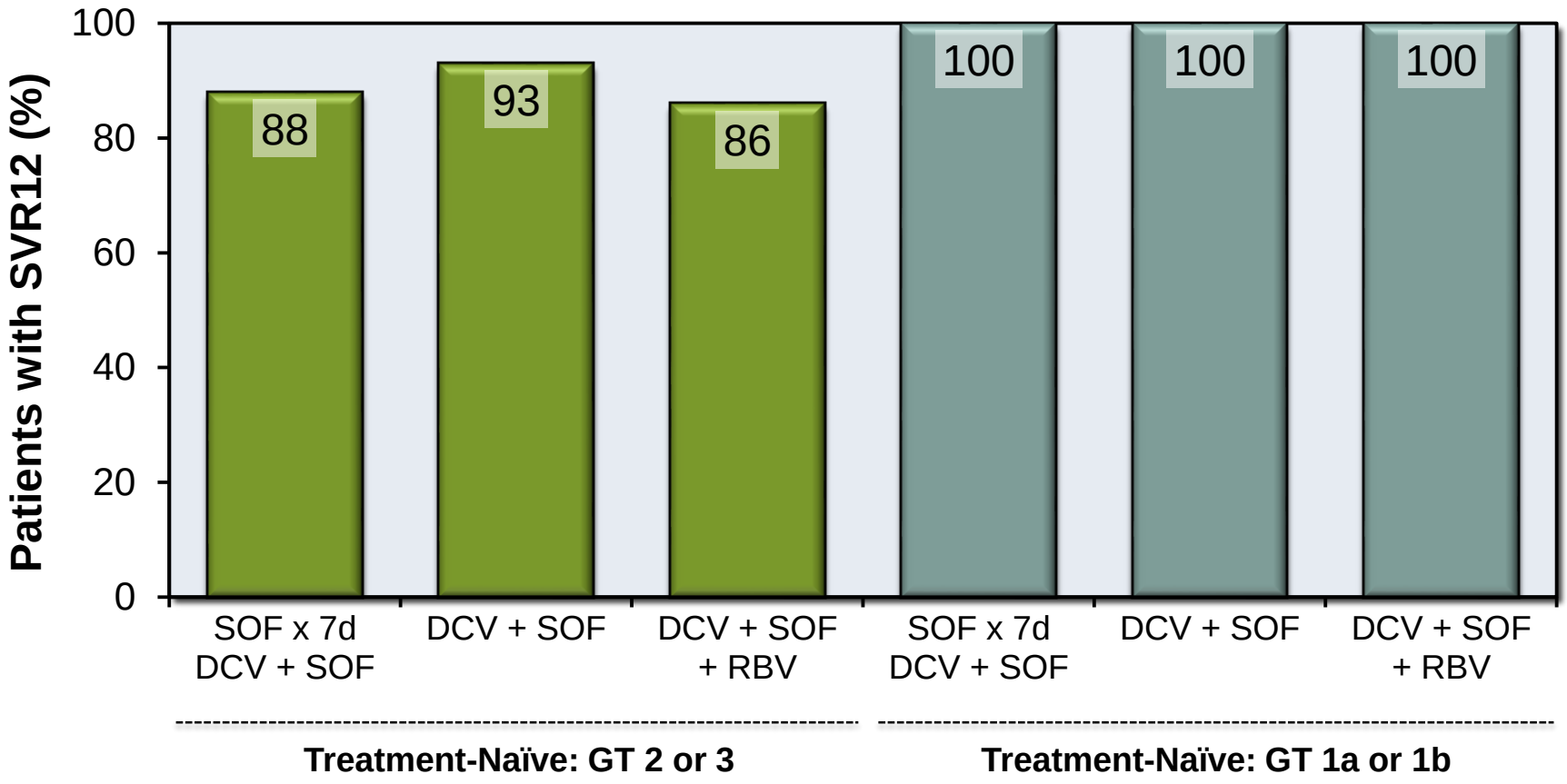
Sofosbuvir (SOF): 400 mg once daily

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.

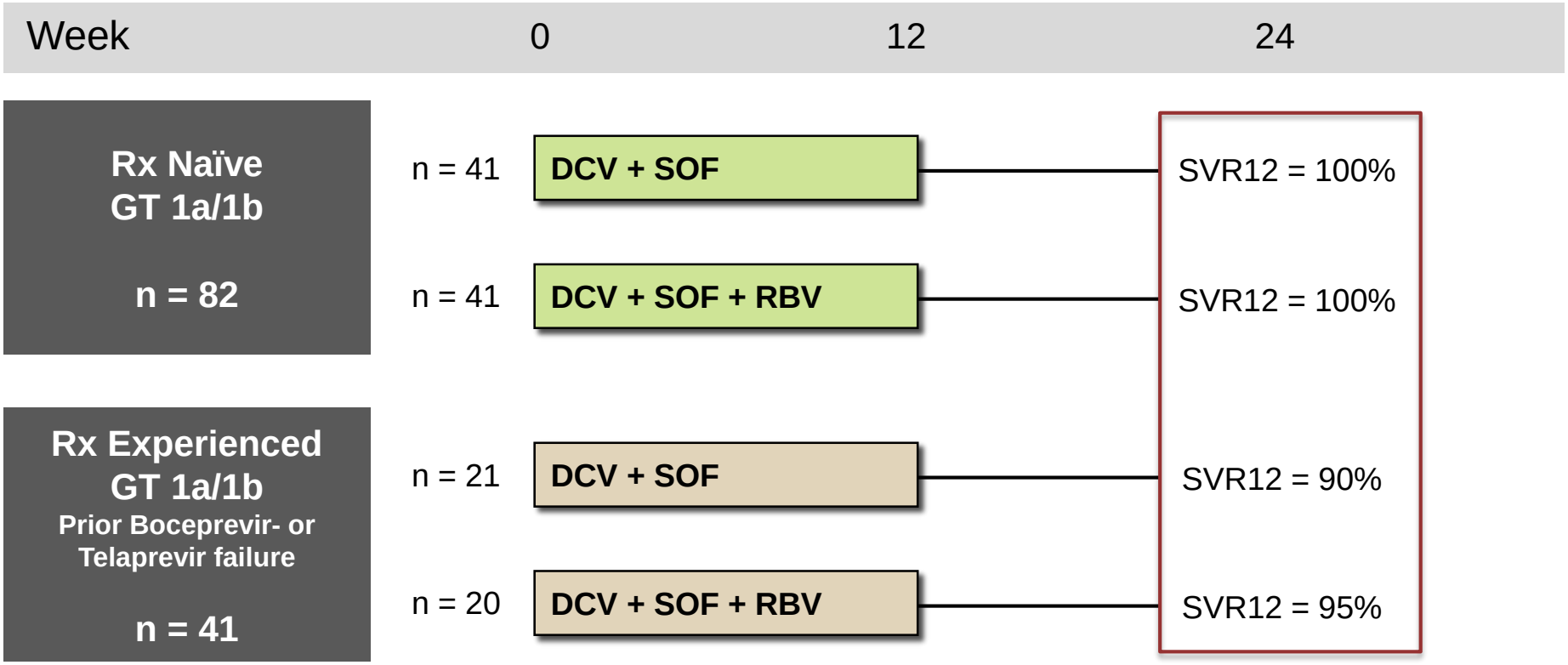
Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Treatment-Naïve 24 Week Rx: Results



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
GT1 Treatment-Naïve & Experienced 12 Week Rx: Results



Drug Dosing

Daclatasvir (DCV): 60 mg once daily

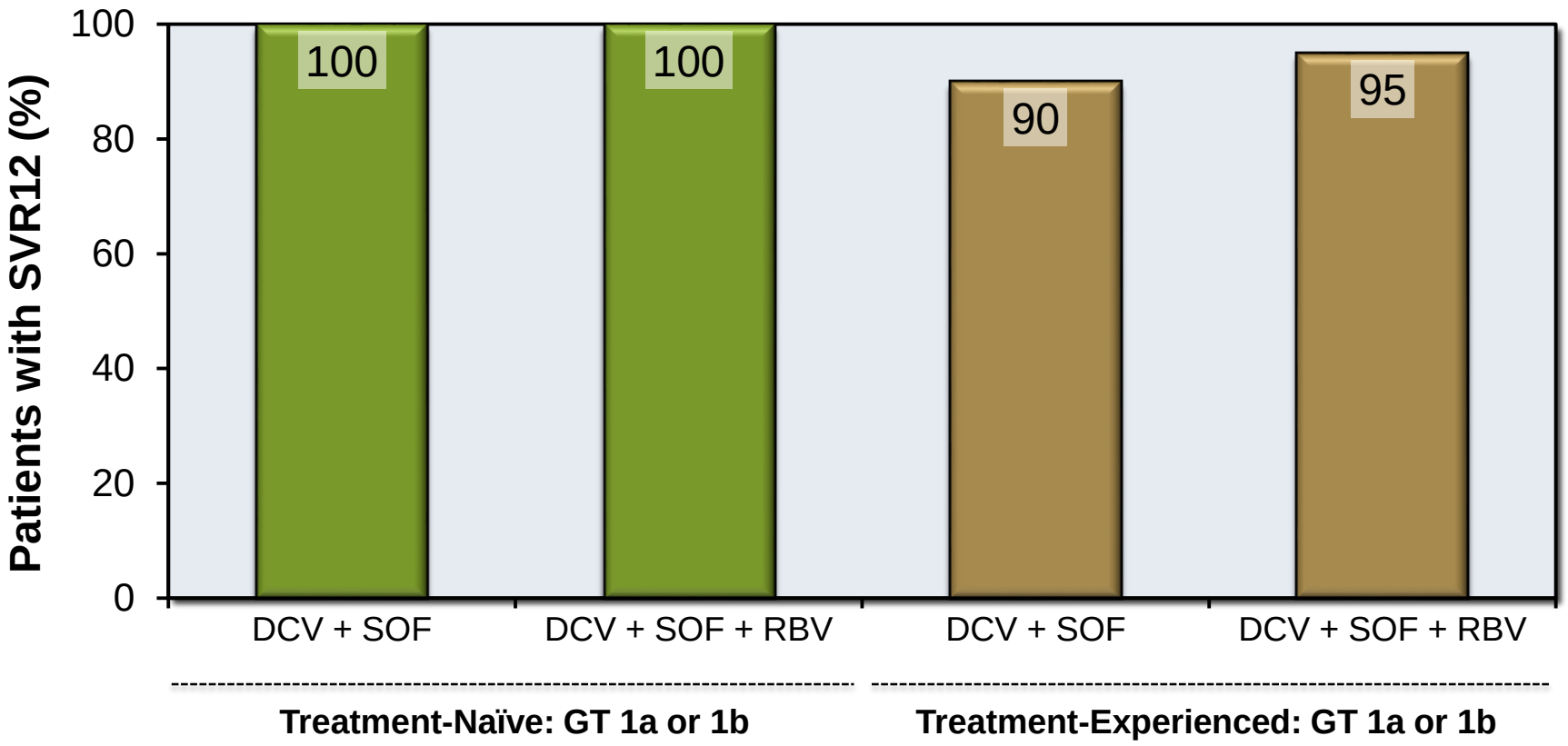
Sofosbuvir (SOF): 400 mg once daily

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 12 Week Rx: Results



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 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.

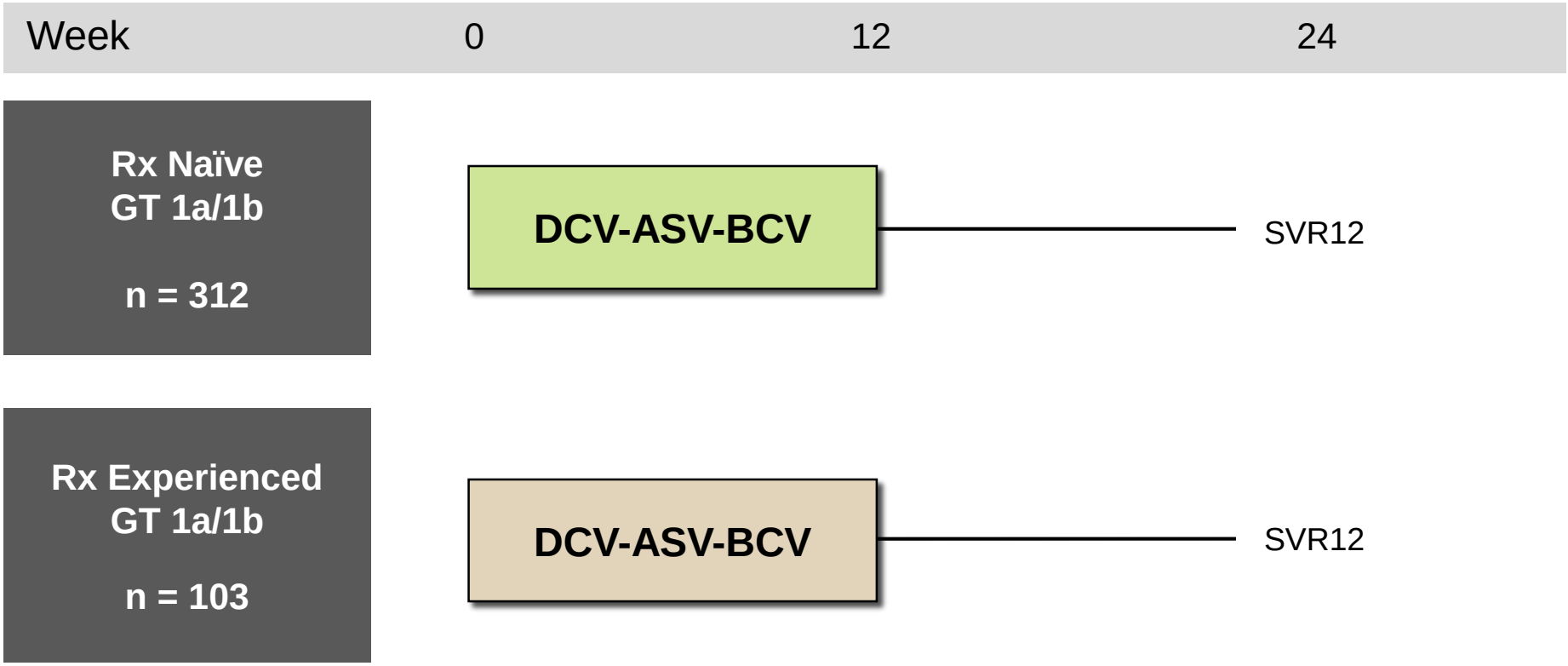
Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Study Features

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 (DCV): 30 mg BID, Asunaprevir (ASV): 200 mg BID and Beclabuvir (BCV): 75 mg BID as fixed-dose combination

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	270 (87%)	91 (88%)
Black	34 (11%)	7 (7%)
Asian	9 (2%)	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	N/A	39 (38%)
Partial response	N/A	12 (12%)
Null response	N/A	25 (24%)
Interferon intolerant	N/A	7 (7%)

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

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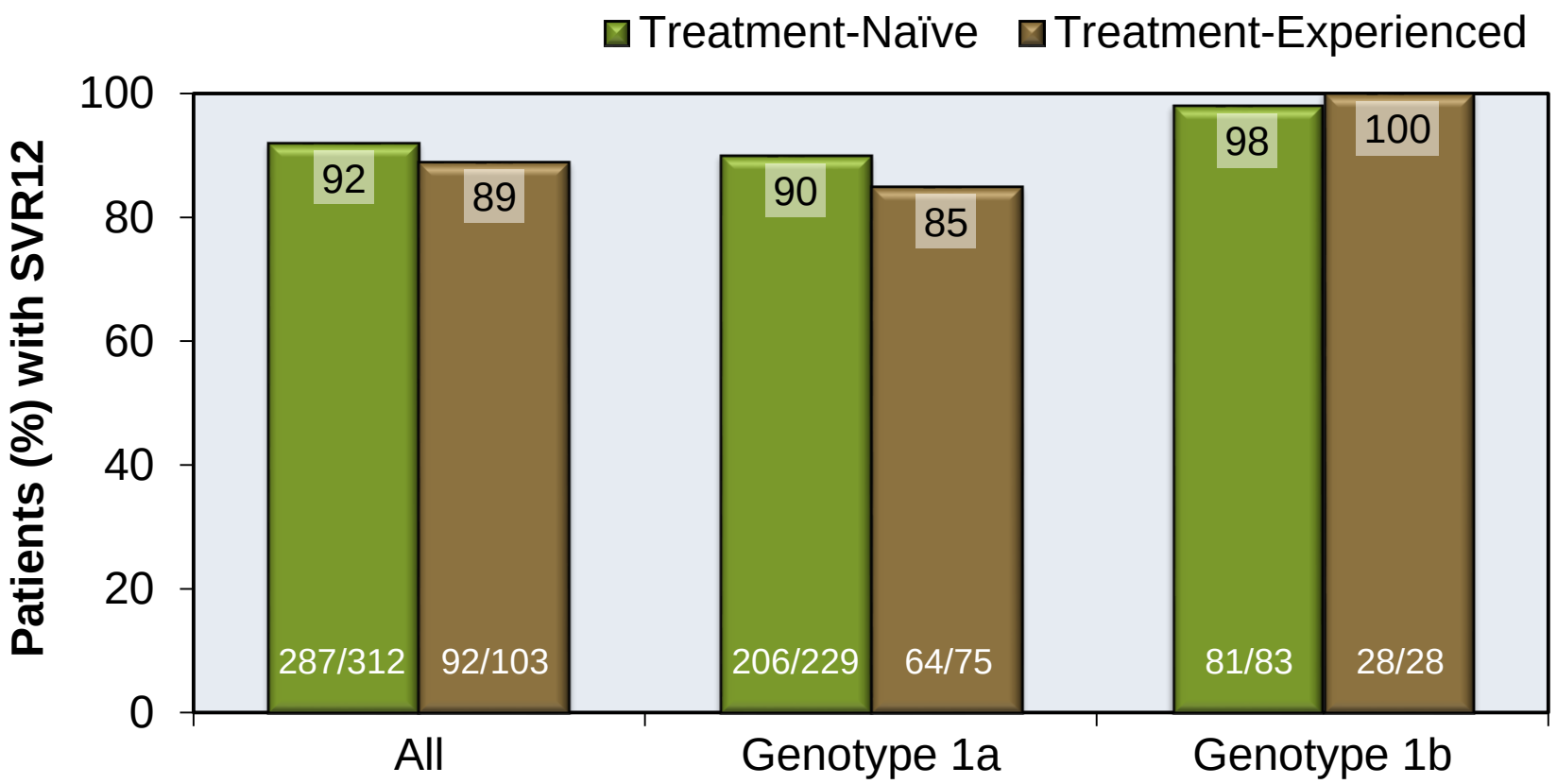
Daclatasvir-Asunaprevir-Beclabuvir for HCV GT 1
UNITY-1 Trial: Results



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.

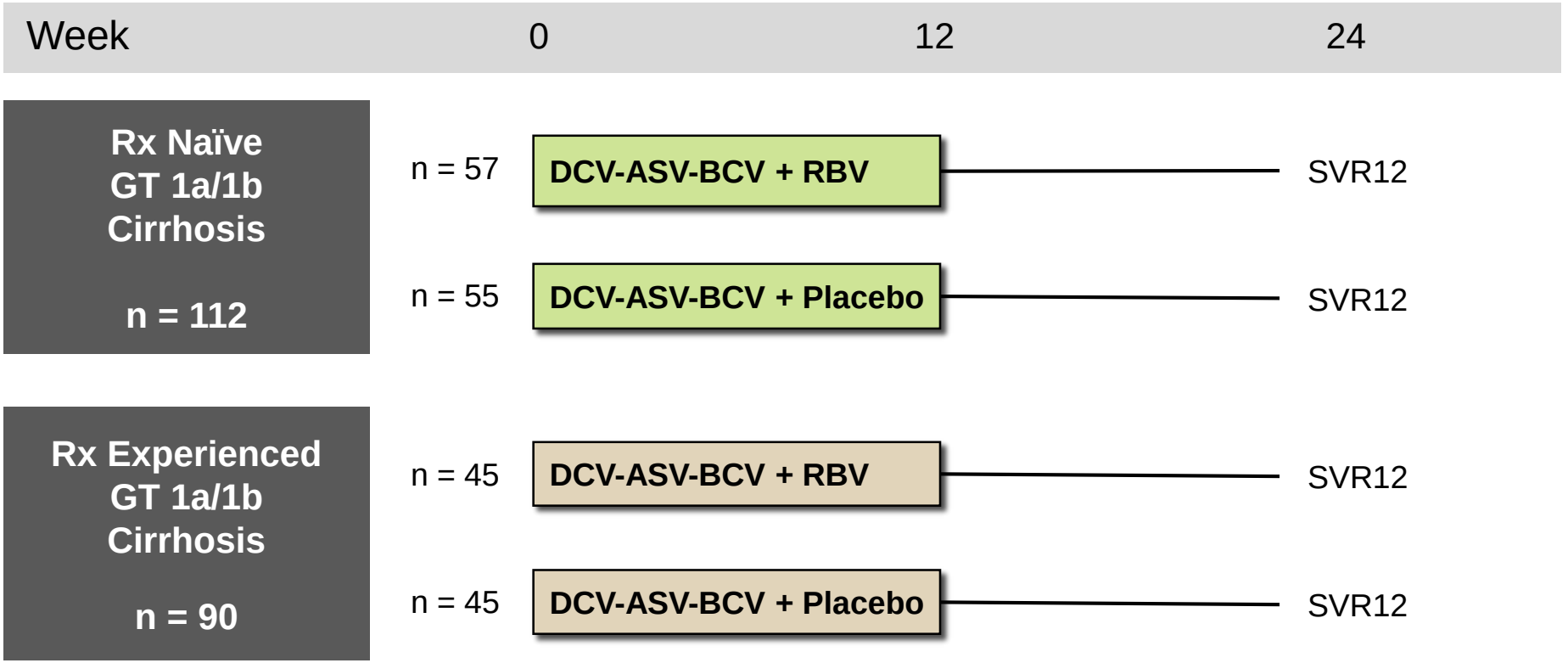
Daclatasvir-Asunaprevir-Beclabuvir +/- RBV for HCV GT 1 UNITY-2 Trial: Study Features

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): 30 mg BID, Asunaprevir (ASV): 200 mg BID and Beclabuvir (BCV): 75 mg BID as fixed-dose combination

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 + Placebo (n=57)
Male	35 (64%)	39 (68%)
Median age, years (range)	59 (35-73)	57 (22-69)
Race White Black Asian	 46 (84%) 6 (11%) 1 (2%)	 49 (88%) 6 (7%) 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

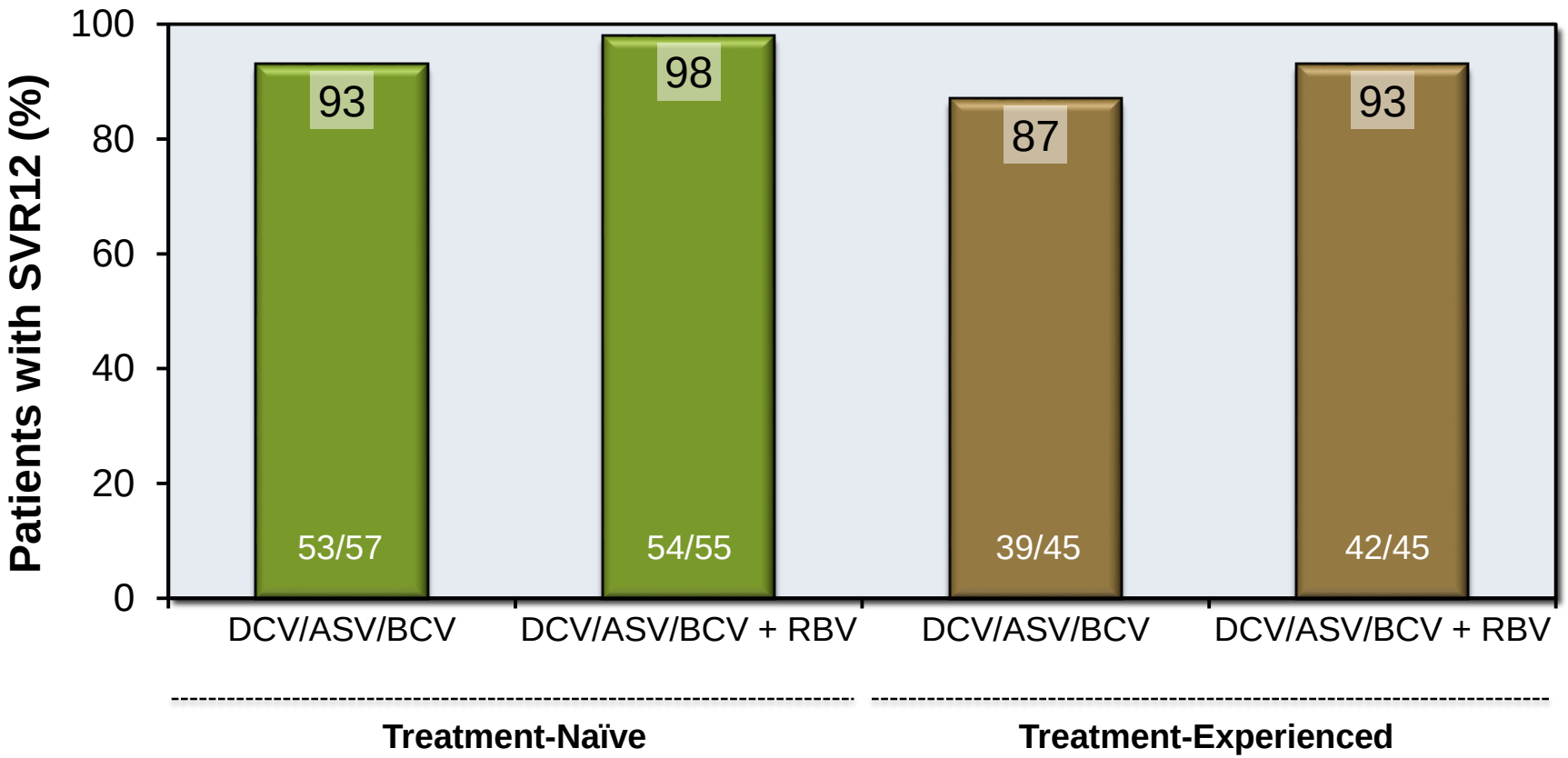
Source: Muir A, et al. JAMA 2015;313:1736-44.

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 + Placebo (n=45)
Male	27 (60%)	32 (71%)
Median age, years (range)	60 (48-73)	59 (19-76)
Race		
White	37 (82%)	41 (91%)
Black	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 (66%)
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

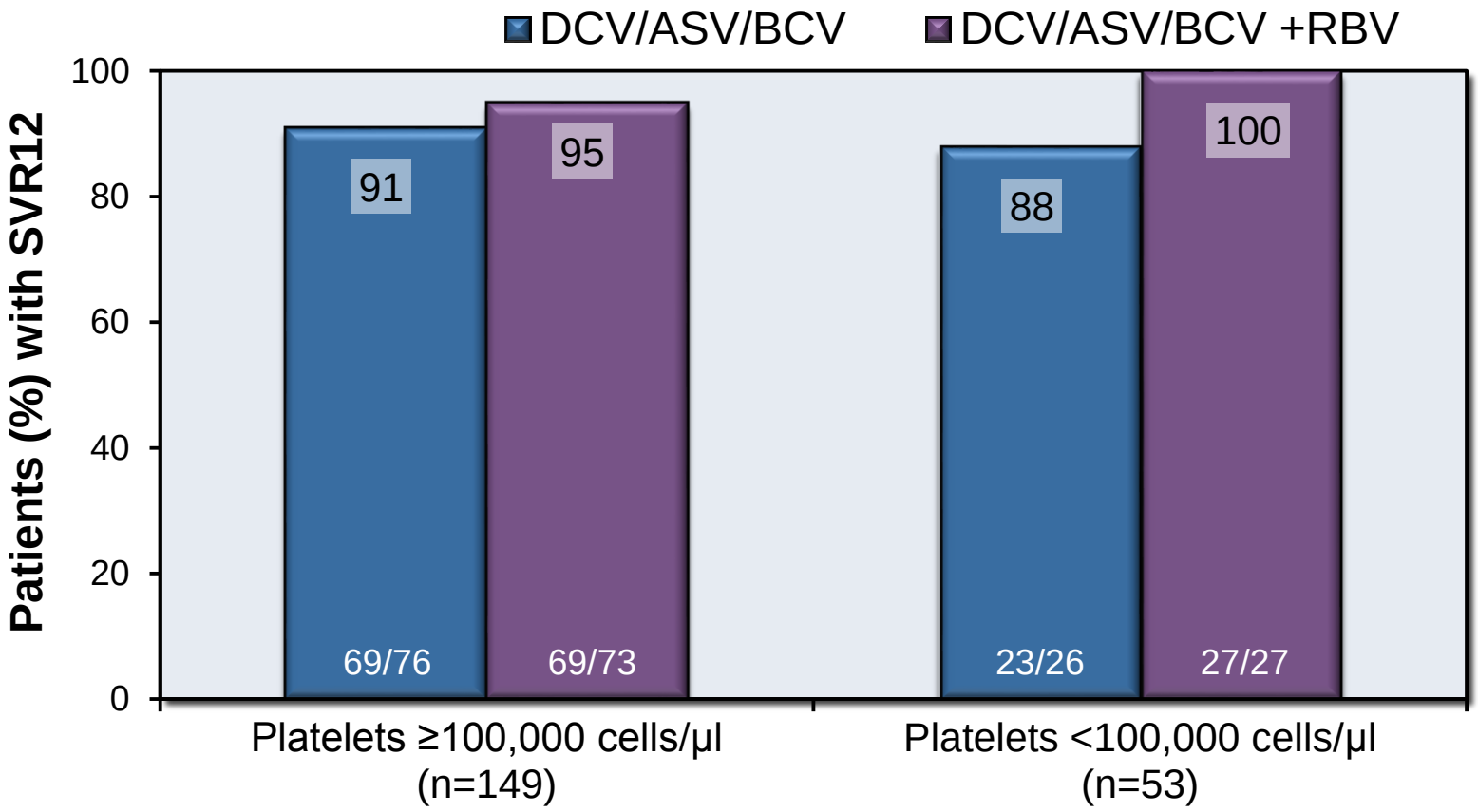


DCV = daclatasvir; ASV = asunaprevir; BCV = beclabuvir; RBV = ribavirin

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



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

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.

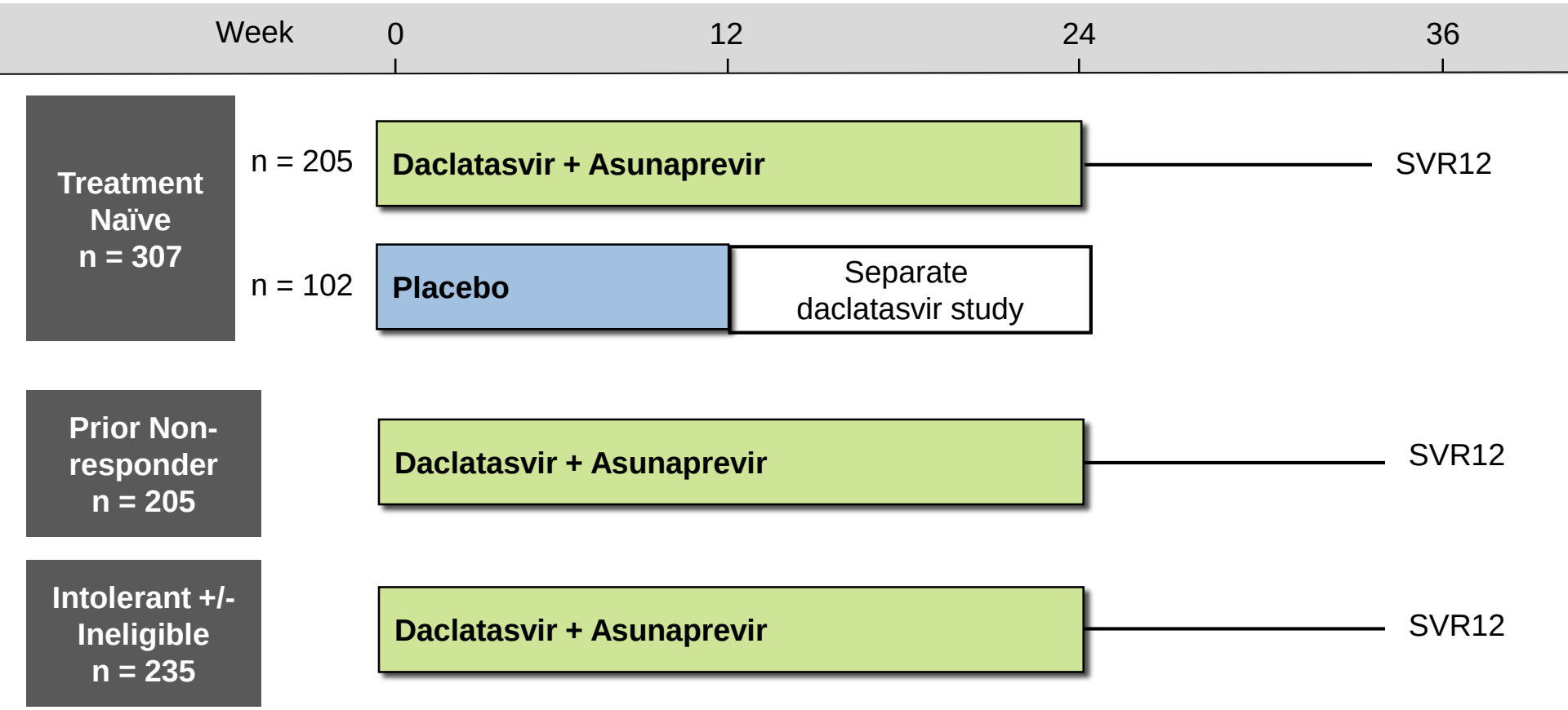
Daclatasvir + Asunaprevir for HCV GT 1b
HALLMARK-DUAL: Study Features

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

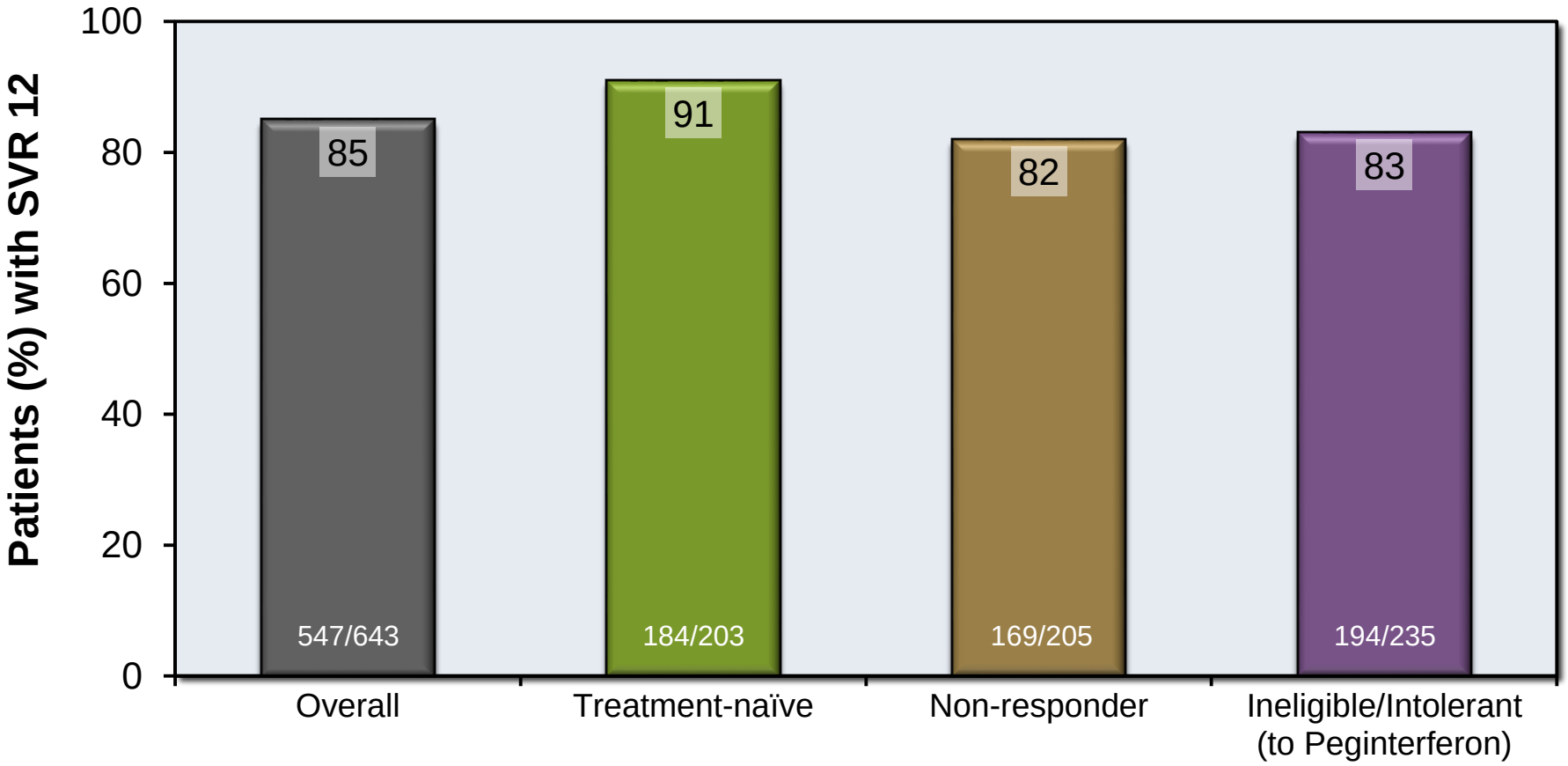
	Treatment-naïve on DCV+ASV (n=205)	Treatment-naïve on Placebo (n=102)	Prior Non-responder (n=205)	Intolerant/Ineligible (n=235)
Age (years)	55 (20-79)	54 (22-83)	58 (23-77)	60 (24-77)
Men	101 (49%)	54 (53%)	111 (54%)	98 (42%)
Race White Black Asian	 135 (66%) 14 (7%) 52 (25%)	 59 (58%) 8 (8%) 45 (22%)	 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

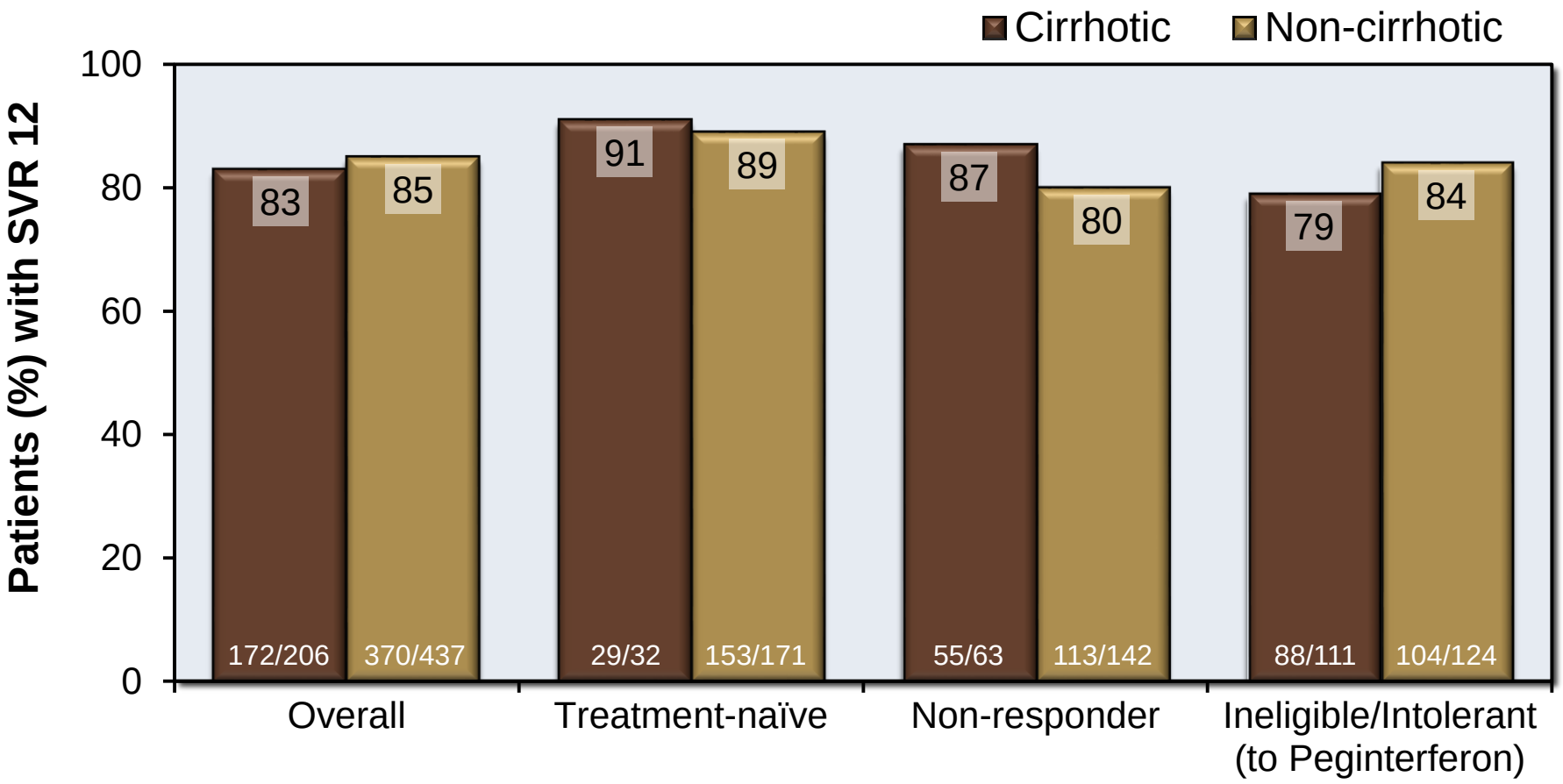
HALLMARK-DUAL: SVR12



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.

Hepatitis web study

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

	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

Conclusions: “In 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.

Treatment-Experienced

Daclatasvir + Asunaprevir + Peg/RBV in Genotype 1 and 4
HALLMARK-QUAD Study

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

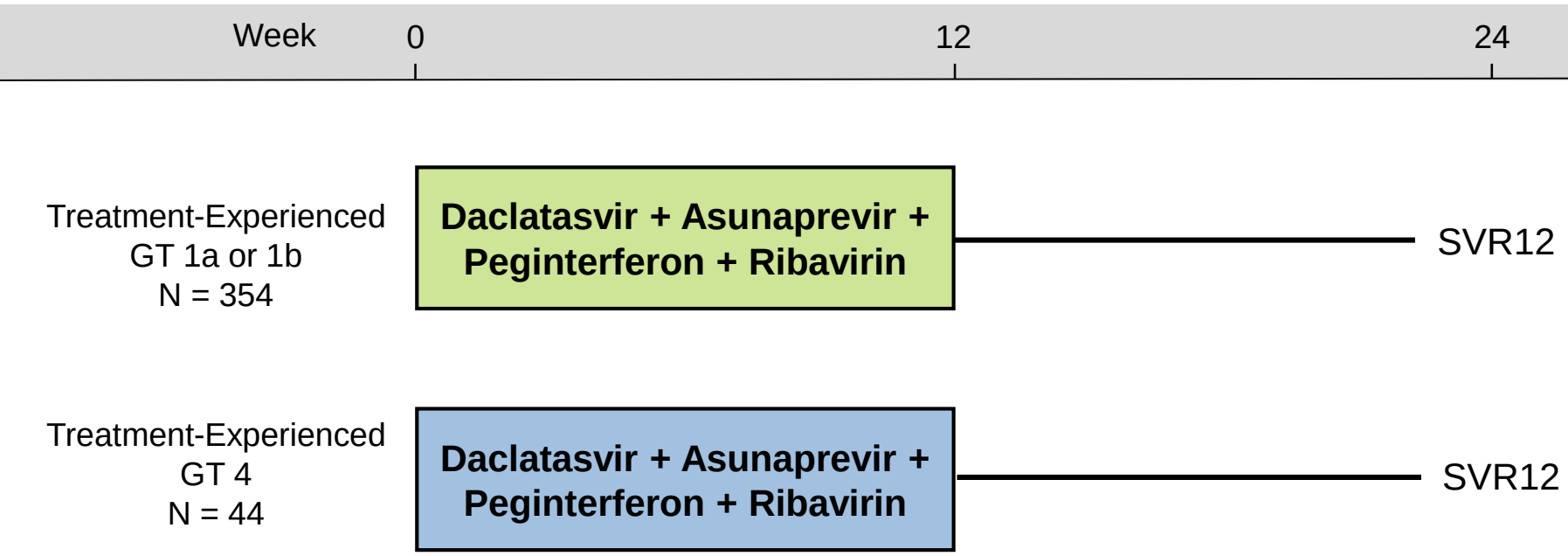
Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Study Features

Daclatasvir + Asunaprevir + PR Trial: 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 DM, 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 DM, et. al. J Hepatol 2015;63:30-7.

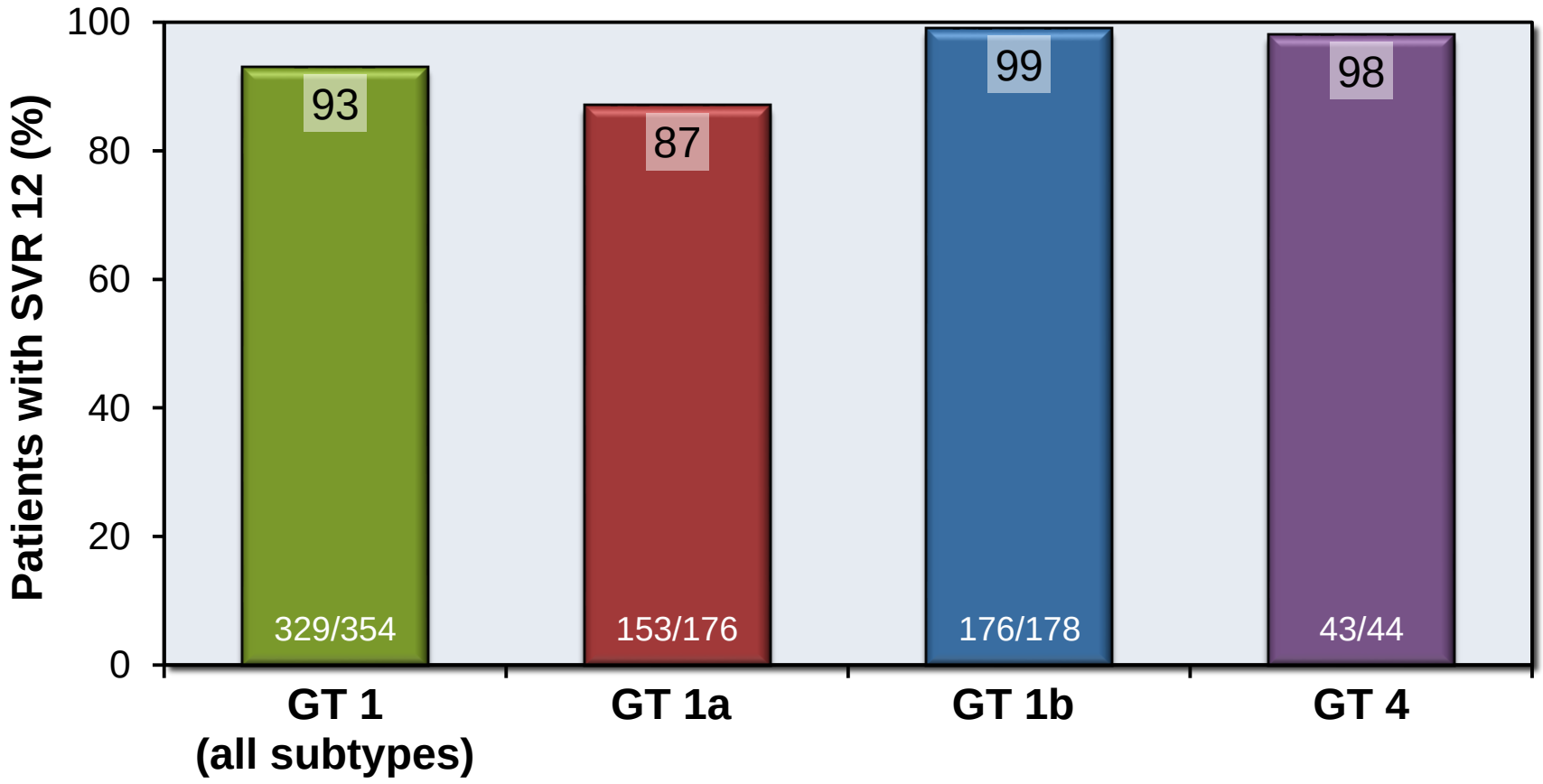
Daclatasvir + Asunaprevir + P/R for HCV GT 1,4
HALLMARK-QUAD Trial: Patient Characteristics

Characteristic	Genotype 1 (n=354)	Genotype 4 (n=44)
Male	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 DM, 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]

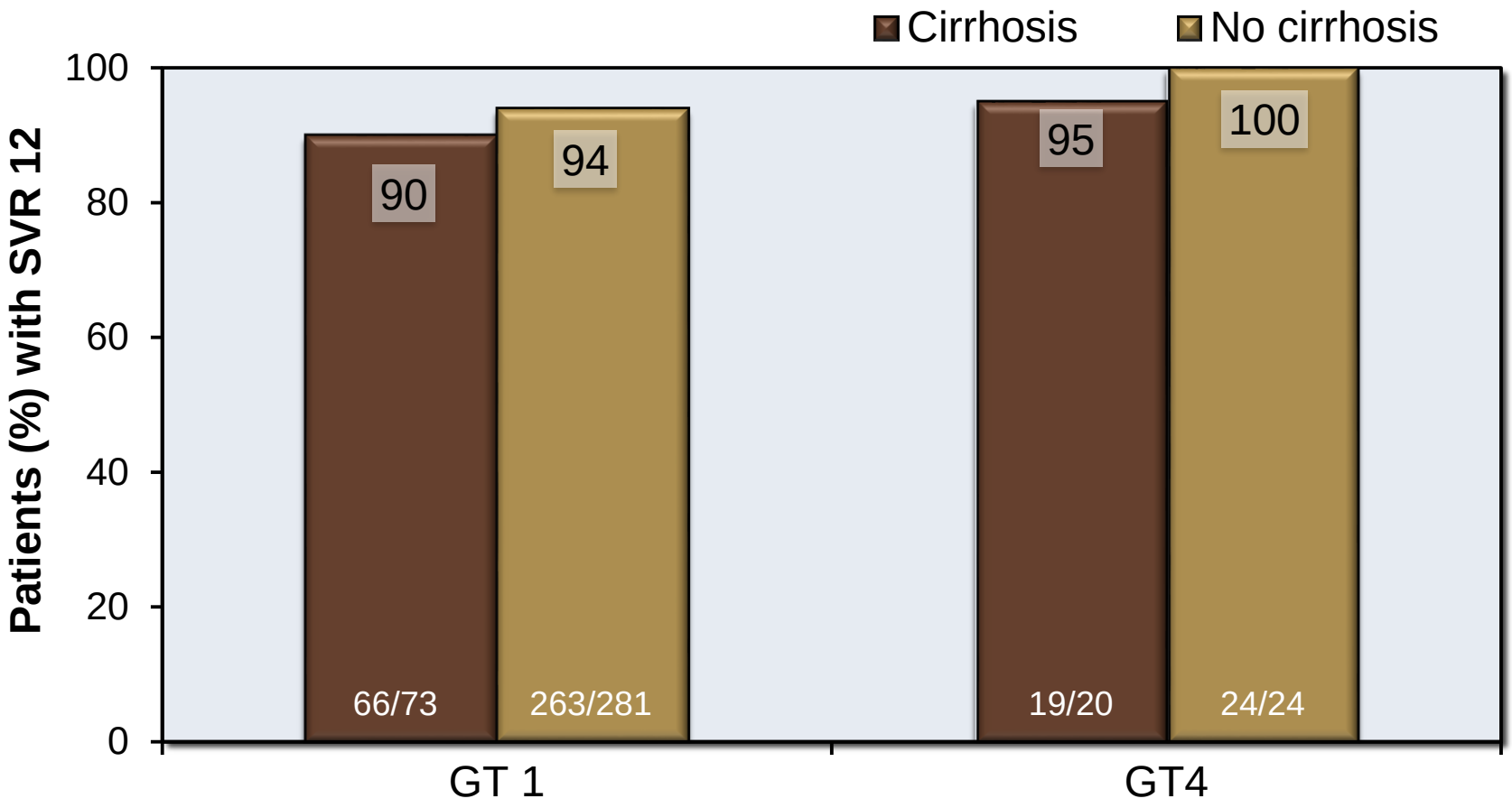


[a] Modified intention-to-treat analysis; GT = genotype

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

Hepatitis web study

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

Treatment-Naïve

Daclatasvir + Peg/RBV in Treatment-Naïve Genotype 4
COMMAND-4 Study

Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

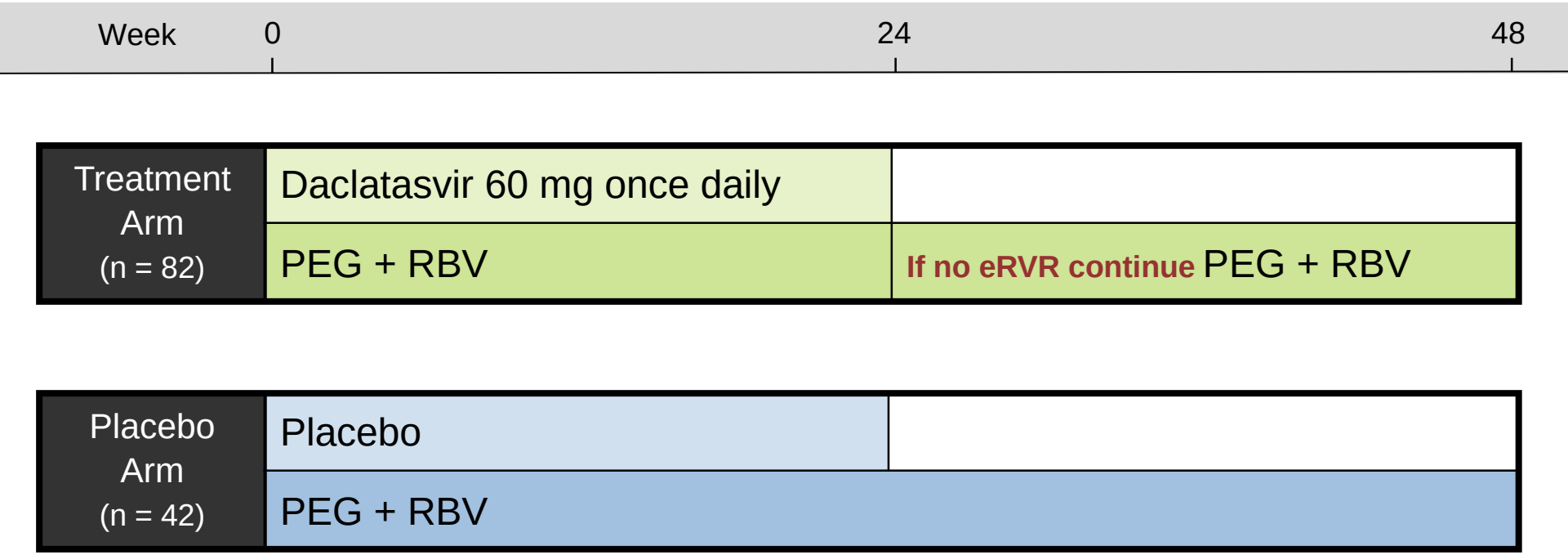
Daclatasvir + Peginterferon/RBV for HCV GT 4
COMMAND-4 Trial: Study Features

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: Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

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: Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

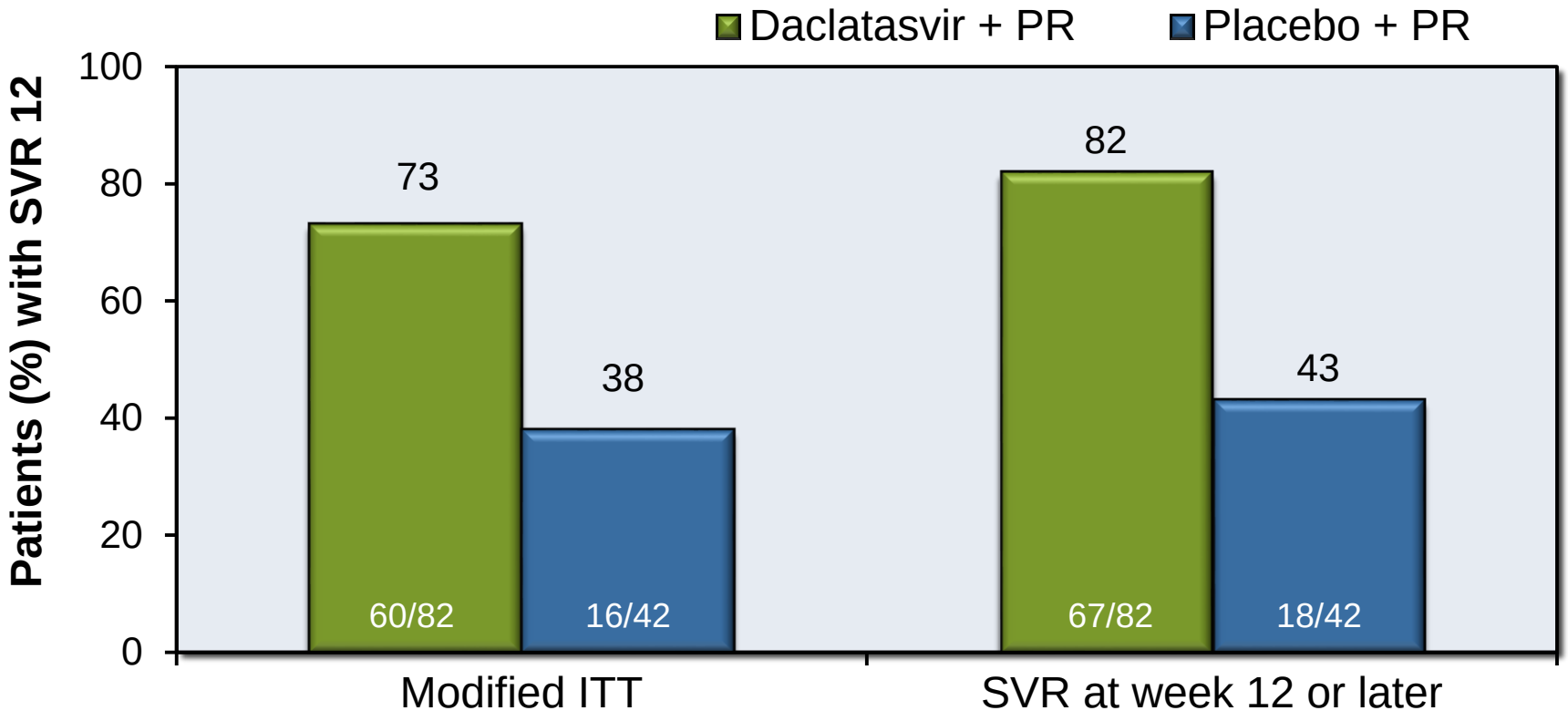
Daclatasvir + Peginterferon/RBV for HCV GT 4 COMMAND-4 Trial: Patient Characteristics

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: Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

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

COMMAND-4: SVR12 by Analysis

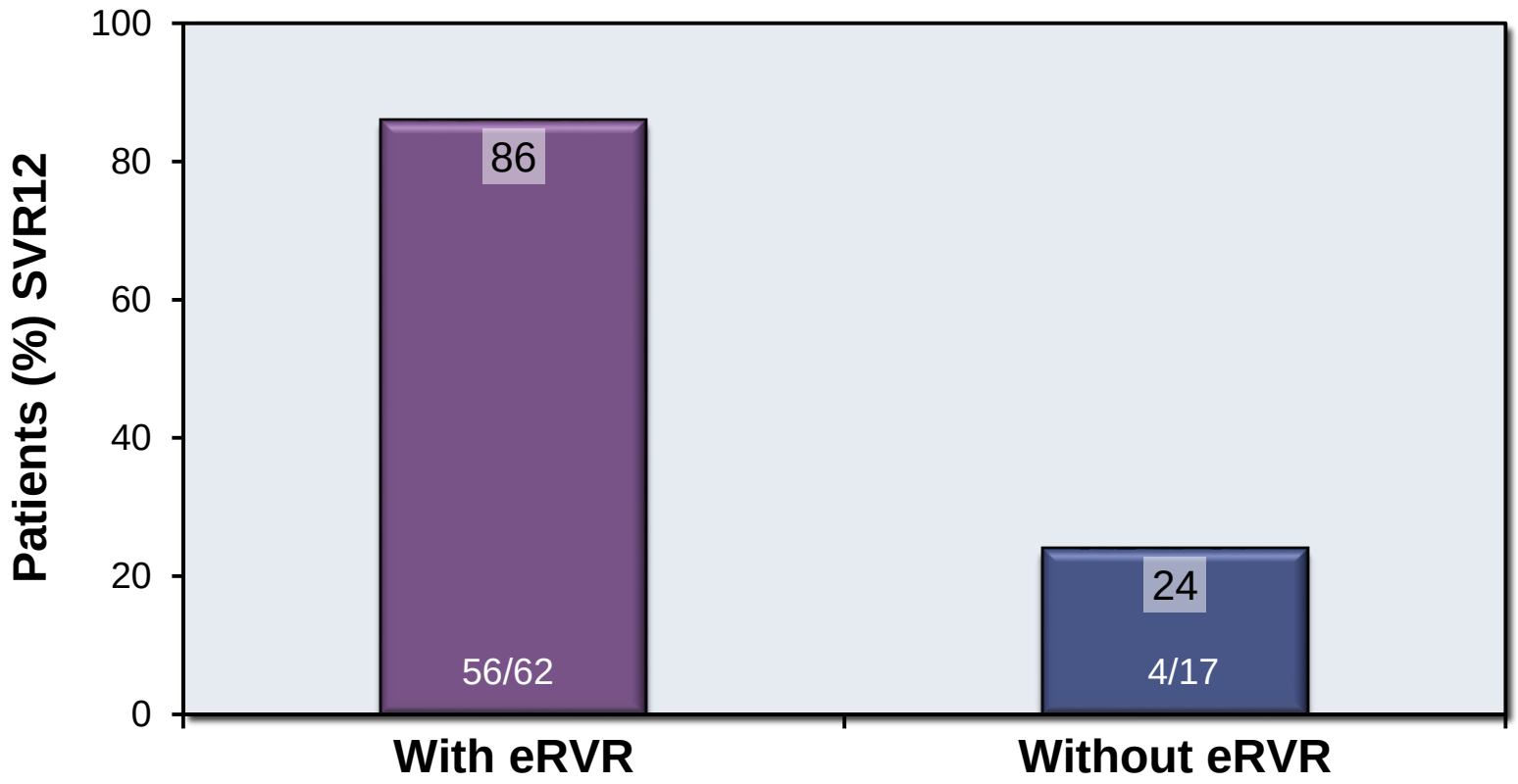


Modified ITT, intent-to-treat: patients with missing data at post-treatment week 12 were considered treatment failures.

Source: Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

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

COMMAND-4: SVR12 by eRVR



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

Source: Hezode C, et. al. ID Week. October 8-12, 2014; Abstract 819.

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 July 21. [Epub ahead of print]

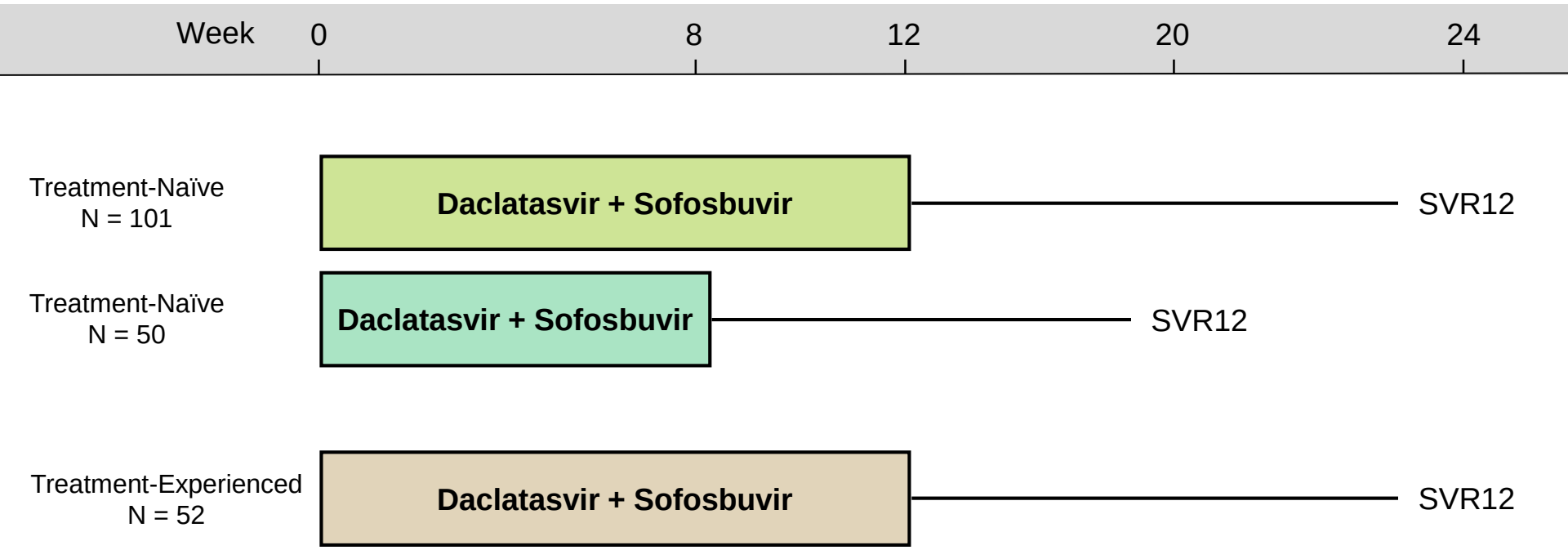
Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: Study Features

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**
  - 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 July 21. [Epub ahead of print]

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 July 21. [Epub ahead of print]

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	92 (91%)	42 (84%)	43 (83%)
Median age, years (range)	52 (24-71)	51 (28-75)	57 (43-66)
Race			
White	66 (65%)	28 (56%)	31 (60%)
Black	30 (30%)	19 (38%)	20 (38%)
Asian/other	5 (5%)	3 (6%)	1 (2%)
HCV genotype			
1A	71 (70%)	35 (70%)	33 (63%)
1B	12 (12%)	6 (12%)	11 (21%)
2	11 (11%)	6 (12%)	2 (4%)
3	6 (6%)	3 (6%)	4 (8%)
4	1 (1%)	0	2 (4%)
Cirrhosis	9 (9%)	5 (10%)	15 (29%)
HCV RNA, median (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 July 21. [Epub ahead of print]

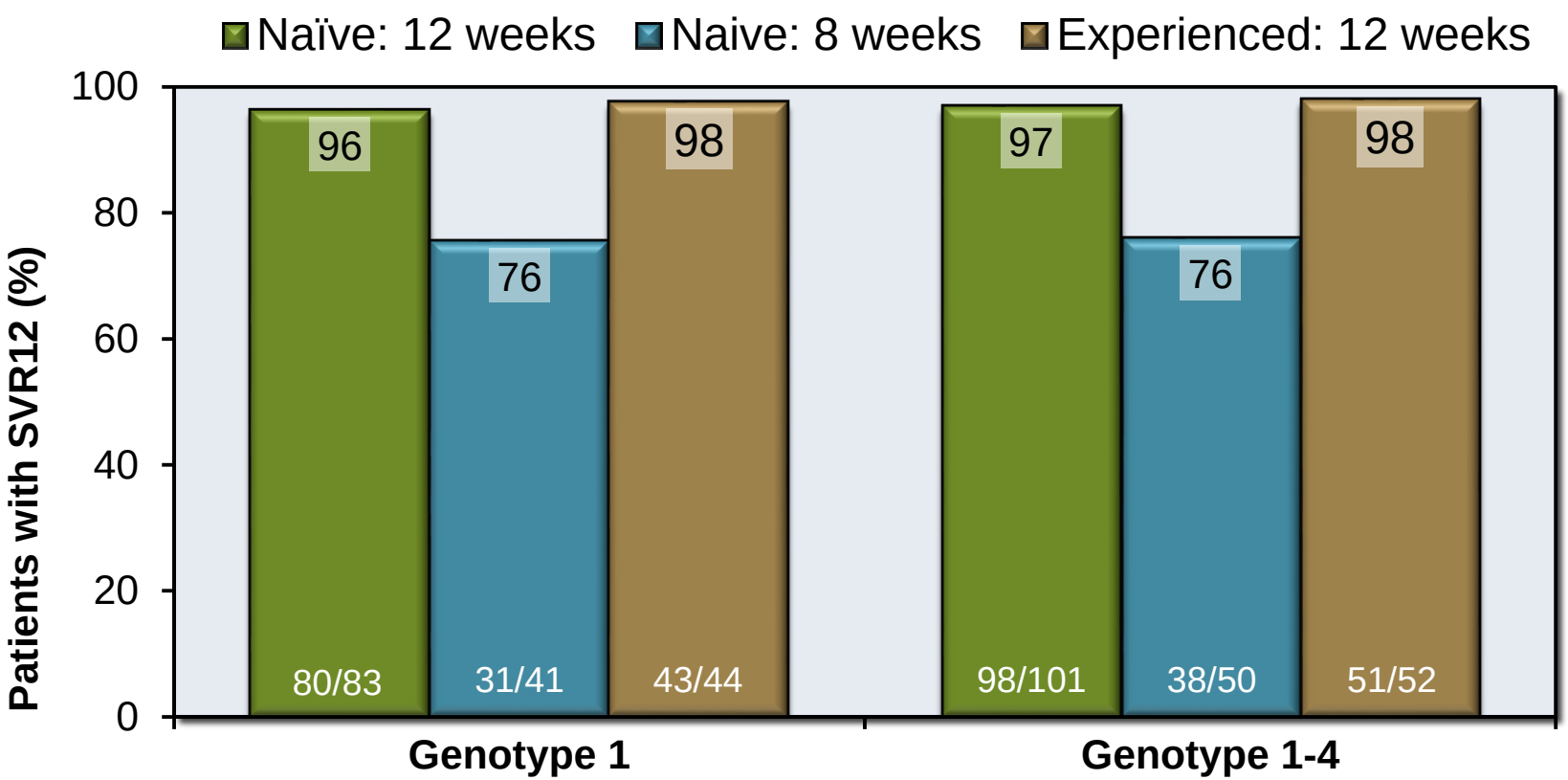
Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection
ALLY-2 Trial: HIV Characteristics

Characteristic	Treatment-Naïve 12-Week Group (n=101)	Treatment-Naïve 8-Week Group (n=50)	Previously Treated 12-Week Group (n=52)
CD4 count, median (range)	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 July 21. [Epub ahead of print]

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

ALLY-2: SVR12, by Prior Treatment Status



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

Source: Wyles DL, et al. N Engl J Med. 2015 July 21. [Epub ahead of print]

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 July 21. [Epub ahead of print]

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/

Funded by a grant from the Centers for Disease Control and Prevention.

Hepatitis web study