HEPATITIS C ONLINE

Elbasvir-Grazoprevir (*Zepatier*)

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Elbasvir-Grazoprevir (*Zepatier*)

Background and Dosing

Elbasvir-Grazoprevir (*Zepatier*)

- **Approval Status**
  - Approval by United States FDA on January 28, 2016
- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotypes 1 or 4 in adults
  - Indicated for treatment of patients with HIV coinfection
- **Class & Mechanism**
  - Elbasvir: HCV NS5A inhibitor
  - Grazoprevir: HCV NS3/4A inhibitor
- **Dosing**
  - Elbasvir-Grazoprevir (fixed dose 50 mg/100 mg) one tablet orally once daily, with or without food
- **Adverse Effects (AE)**
  - Fatigue, headache, and nausea
  - Increase in ALT > 5x normal in 1% of subjects

Source: *Zepatier* Prescribing Information. Merck & Co., Inc.

Elbasvir-Grazoprevir (*Zepatier*) Indications and Usage

Elbasvir-Grazoprevir (EBR-GZR) HCV Treatment in Patients with or without Cirrhosis		
Patient Population	**Treatment**	**Duration**
GT 1a: Treatment-naïve or PegIFN/RBV-experienced (without baseline NS5A polymorphisms*)	Elbasvir-Grazoprevir	12 weeks
GT 1a: Treatment-naïve or PegIFN/RBV-experienced (with baseline NS5A polymorphisms*)	Elbasvir-Grazoprevir + RBV	16 weeks
GT 1b: Treatment-naïve or PegIFN/RBV-experienced	Elbasvir-Grazoprevir	12 weeks
GT 1a or 1b: PegIFN/RBV/PI-experienced	Elbasvir-Grazoprevir + RBV	12 weeks
GT 4: Treatment-naïve	Elbasvir-Grazoprevir	12 weeks
GT 4: PegIFN/RBV-Experienced	Elbasvir-Grazoprevir + RBV	16 weeks

Abbreviations: PegIFN = peginterferon; RBV = ribavirin; PI = protease inhibitor; EBR-GZR = elbasvir-grazoprevir
*Polymorphisms at amino acid positions 28, 30, 31, or 93

Source: *Zepatier* Prescribing Information. Merck & Co., Inc.

Elbasvir-Grazoprevir (*Zepatier*)
HCV GT1a and Impact of Baseline NS5A Polymorphisms on SVR12

HCV GT1a and Impact of Baseline NS5A Polymorphisms on SVR12

NS5A Polymorphism Status	**EBR-GZR x 12 weeks** SVR12% (n/N)	**EBR-GZR + RBV x 16 weeks** SVR12% (n/N)
Without baseline NS5A polymorphism (M28, Q30, L31, or Y93)	98% (441/450)	100% (49/49)
With baseline NS5A polymorphism (M28*, Q30*, L31*, or Y93*)	70% (39/56)	100% (6/6)

Abbreviations: GT = genotype; EBR = elbasvir; GZR = grazoprevir
*Any change from GT1a reference

Source: *Zepatier* Prescribing Information. Merck & Co., Inc.

Elbasvir-Grazoprevir (EBR-GZR): Summary of Key Phase 3 Trials

- **C-EDGE TN**: EBR-GZR x 12 weeks in TN, GT 1, 4, or 6
- **C-EDGE TE**: EBR-GZR +/- RBV x 12 or 16 weeks in TE, GT 1, 4 or 6
- **Pooled Analysis GT4**: EBR-GZR x 12 weeks in TN & TE GT 4
- **C-EDGE Coinfection**: EBR-GZR x 12 weeks in HCV-HIV coinfection
- **C-EDGE CO-STAR**: EBR-GZR x 12 weeks in persons who inject drugs
- **C-SURFER**: EBR-GZR x 12 weeks in GT1 and Chronic kidney disease
- **Integrated Analysis with Compensated Cirrhosis**: EBR-GZR, GT 1, 4 or 6

Abbreviations: EBR-GZR = elbasvir-grazoprevir; TN = treatment naïve; GT = genotype; TE = treatment experienced; RBV = ribavirin

Elbasvir-Grazoprevir in Treatment-Naïve Patients

Elbasvir-Grazoprevir in Treatment-Naïve HCV Genotype 1, 4, or 6

C-EDGE: Treatment Naïve

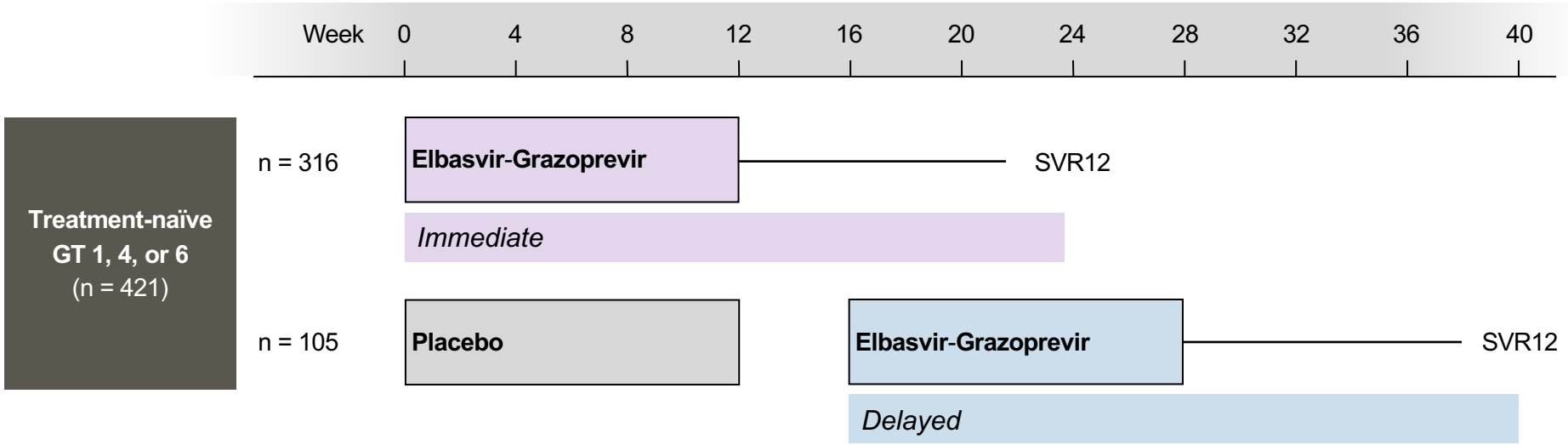
Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV Genotype 1, 4, or 6
C-EDGE TN: Features

- **Design**: Randomized, placebo-controlled, parallel-group, phase 3 trial using a fixed-dose combination of elbasvir-grazoprevir for 12 weeks in treatment-naïve patients with GT 1, 4, or 6 chronic HCV
- **Setting**: 60 sites in United States, Europe, Australia, Scandinavia, & Asia
- **Entry Criteria**
  - Chronic HCV: GT1 = 91%, GT4 = 6%, or GT6 = 3%
  - Age 18 years or older
  - HCV RNA ≥10,000 IU/mL
  - No prior HCV treatment
  - Patients with compensated cirrhosis accepted
- **Primary End-Point**: SVR12

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV Genotype 1, 4, or 6
C-EDGE TN: Design



Randomized 3:1 ratio to immediate or deferred arm; stratified by cirrhosis, HCV genotype, subtype
After 4 weeks of follow-up, placebo recipients unblinded and given elbasvir-grazoprevir open label

Drug Dosing
Elbasvir-Grazoprevir (50/100 mg): fixed dose combination; one pill once daily

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

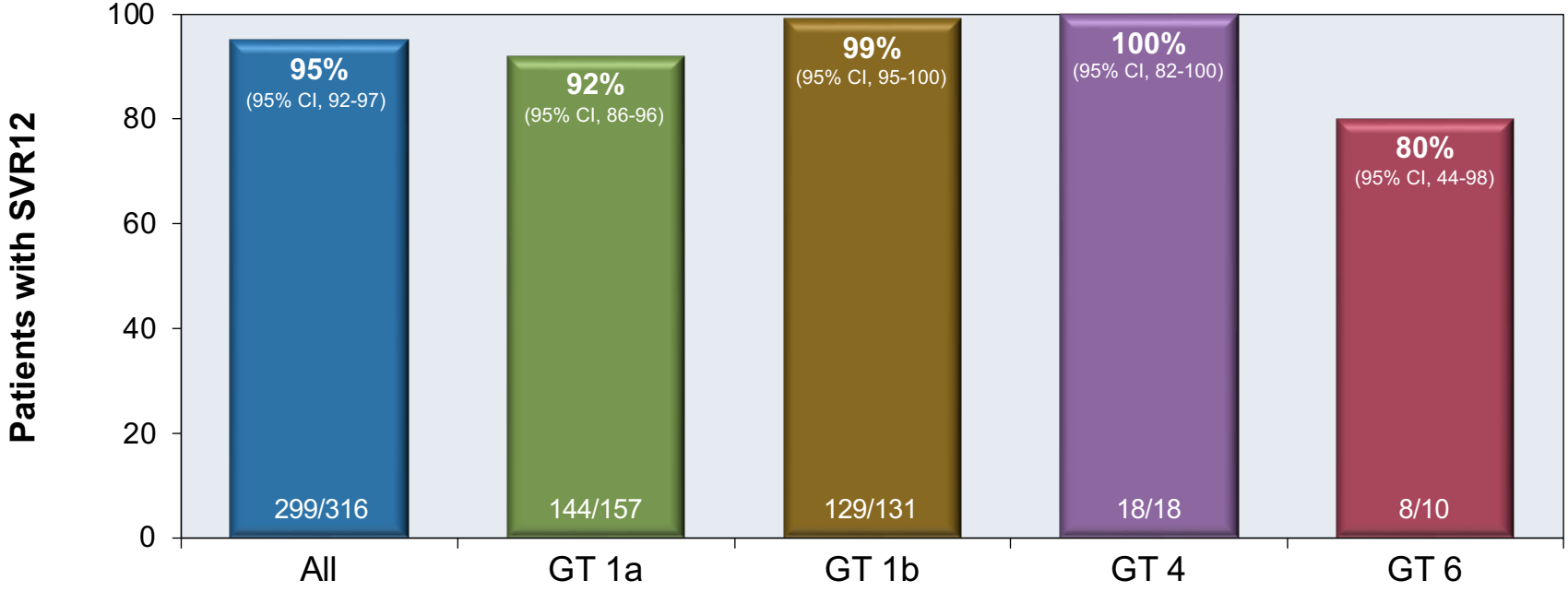
Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Baseline Characteristics

Baseline Characteristic	Immediate Arm (n = 316)	Delayed Arm (n = 105)	All Patients (n = 421)
Age, mean	52	54	53
Male, %	54	53	54
Race, %			
Asian	17	12	16
Black	19	17	18
White	60	70	63
HCV genotype, n (%)			
1a	157 (50)	54 (51)	211 (50)
1b	131 (42)	40 (38)	171 (41)
4	18 (6)	8 (8)	26 (6)
6	10 (3)	3 (3)	13 (3)
HCV RNA >800,000 IU/ml, %	222 (70)	66 (63)	288 (68)
IL28B non-CC, %	66	64	65
Fibrosis stage, %			
F0-2	67	66	66
F3	11	13	12
F4	22	21	22

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Results for Immediate Group

C-EDGE TN: SVR12 Results by Genotype

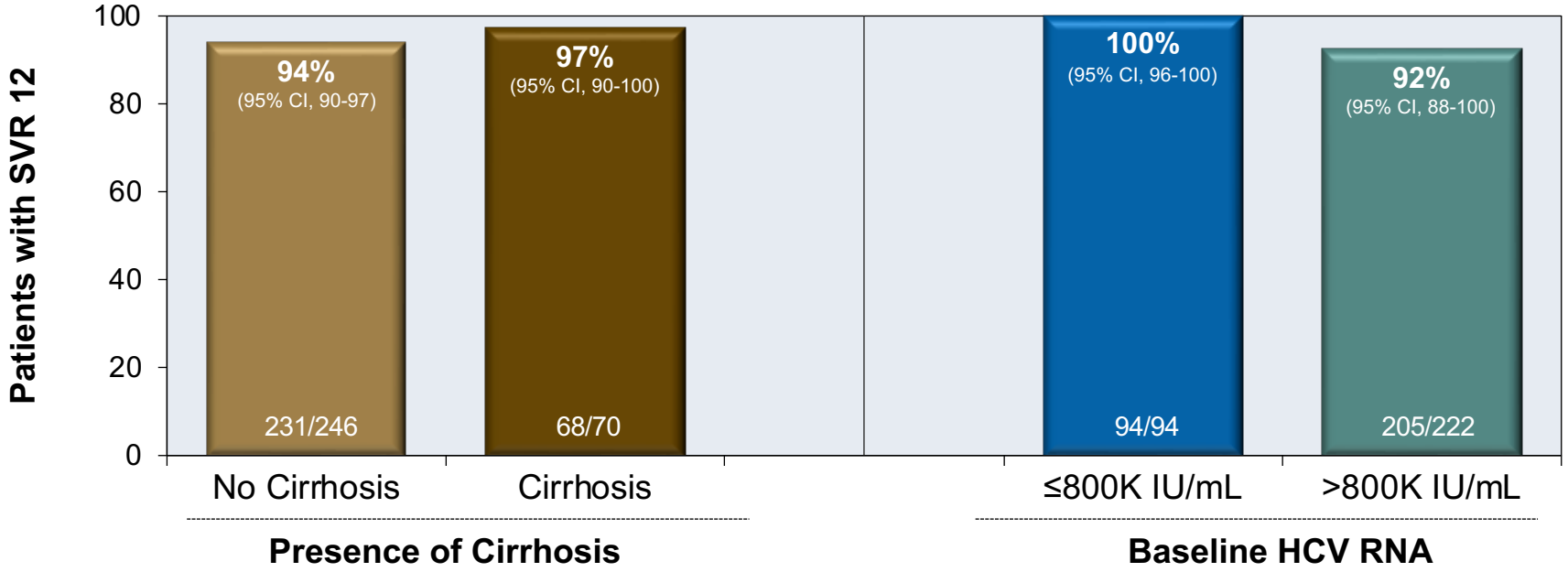


Primary efficacy analysis included all patients who received ≥1 dose of drug.

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Results for Immediate Group

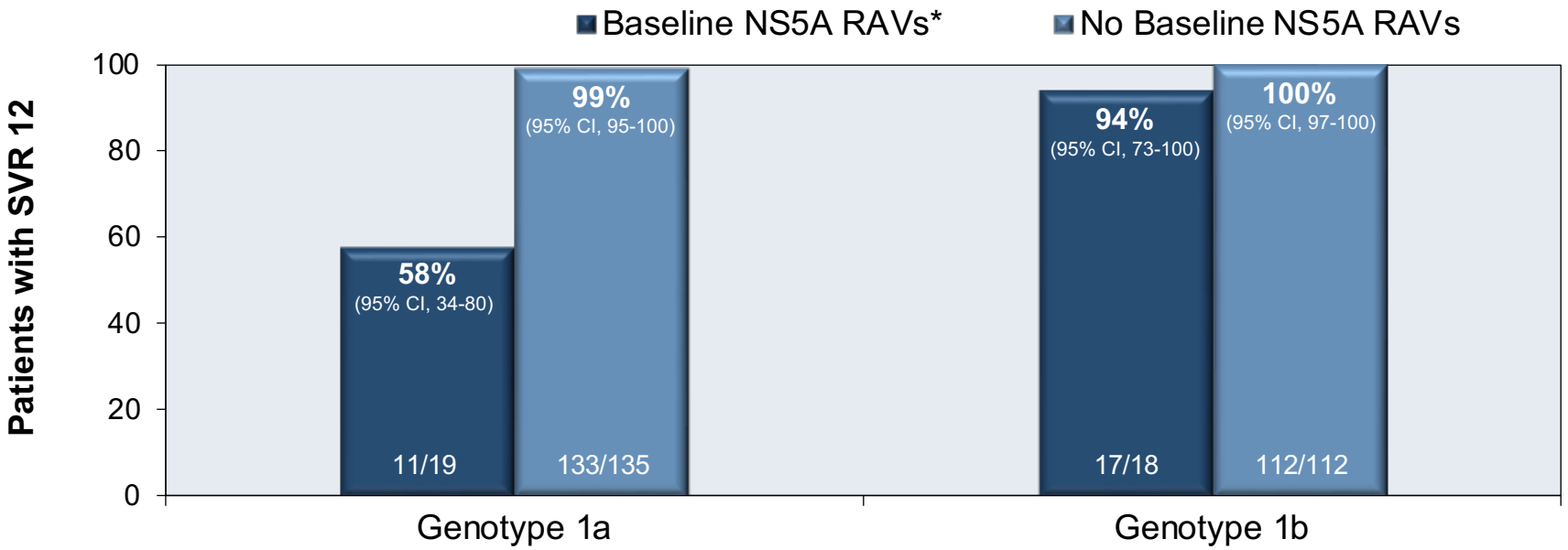
C-EDGE TN: SVR12 by Presence of Cirrhosis or High HCV RNA Level



Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Results

Baseline NS5A Resistance-Associated Variants and SVR12 in GT1

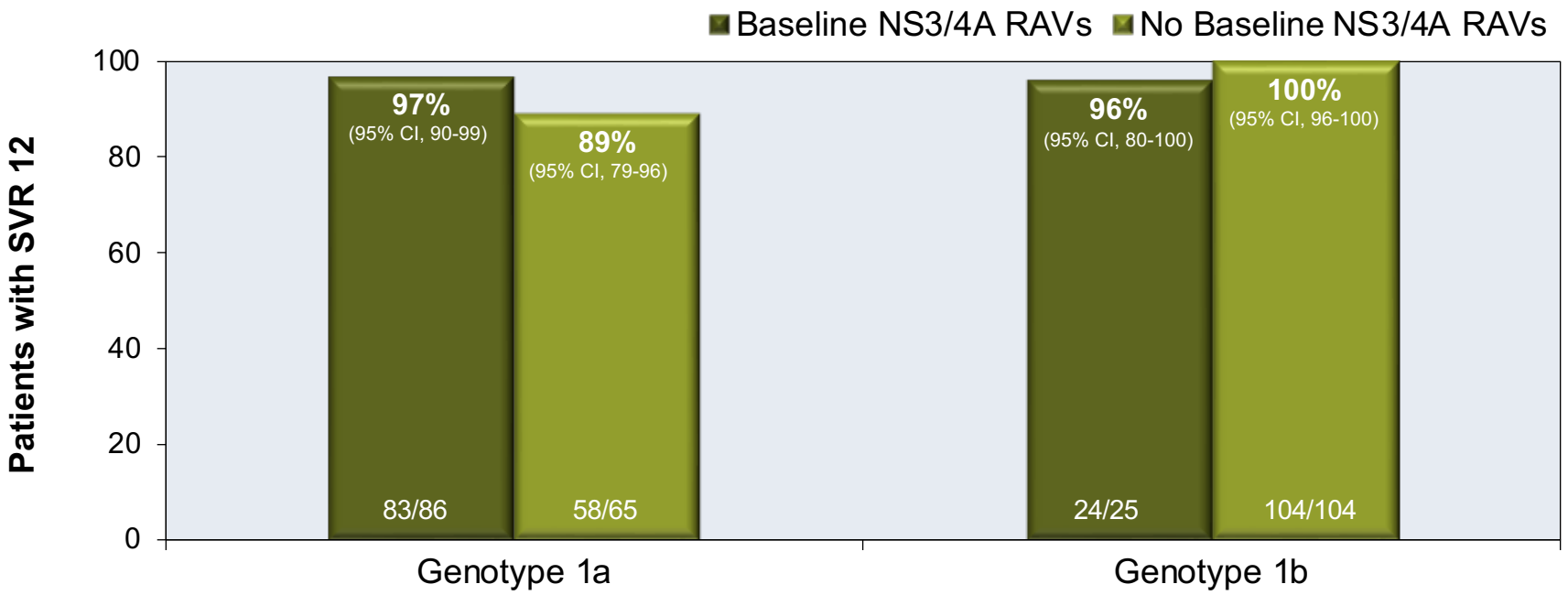


*Patients with baseline GT1a RAVs with a ≤5-fold shift to elbasvir: SVR12=90% (9 of 10)
*Patients with baseline GT1a RAVs with a >5-fold shift to elbasvir: SVR12=22% (2 of 9)

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Results

Baseline NS3/4A Resistance-Associated Variants and SVR12 in GT1



Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4 or 6
C-EDGE TN: Adverse Events

Adverse Event (AE)	Elbasvir-Grazoprevir	
	Immediate (n = 316)	**Delayed** (Placebo) (n = 105)
Discontinuation due to AE	3 (0.9%)	1 (1%)
Serious AEs	9 (3%)	3 (3%)
Deaths	2 (0.6%)[§]	0
Any AE in ≥10% of patients		
Headache	52 (17%)	19 (18%)
Fatigue	49 (16%)	18 (17%)
Laboratory AEs		
ALT >5 x baseline	3 (0.9%)	0
AST >5 x baseline	1 (0.3%)	0
Total bilirubin elevation >5 x baseline	1 (0.3%)	0
Grade 3 or 4 hemoglobin	0	0
Grade 3 or 4 neutrophils	1 (0.3%)	1 (1%)
Grade 3 or 4 creatinine	0	0

[§]Neither death was considered to be study-related.

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4, or 6
C-EDGE TN: Conclusions

Conclusions: “Grazoprevir-elbasvir achieved high SVR12 rates in treatment-naive cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. This once-daily, all-oral, fixed-combination regimen represents a potent new therapeutic option for chronic HCV infection.”

Source: Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Elbasvir-Grazoprevir in Treatment-Experienced Patients

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6

C-EDGE: Treatment Experienced

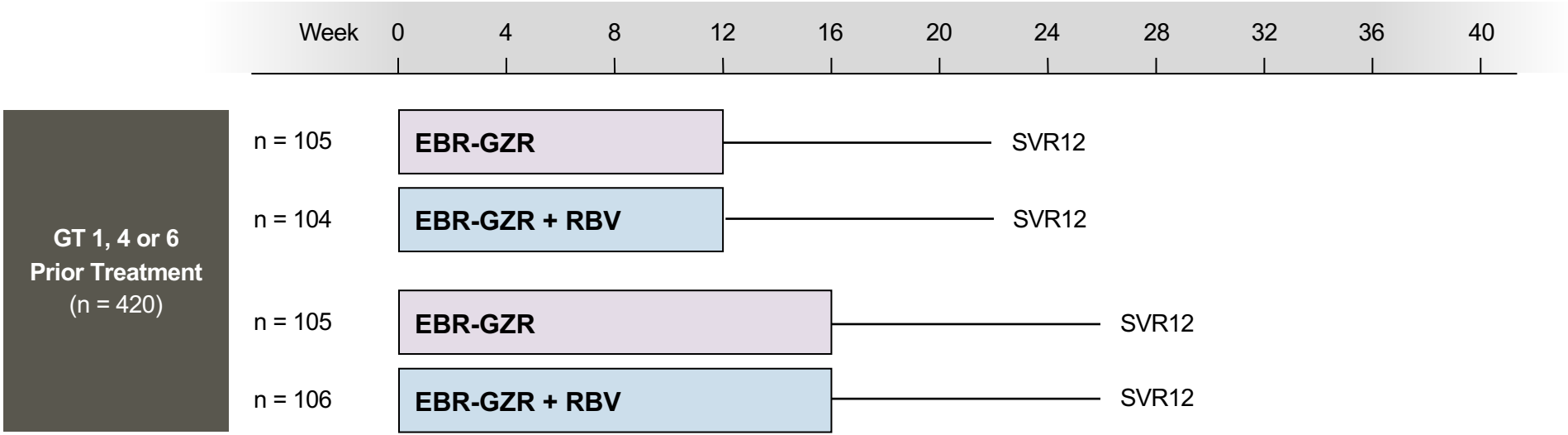
Source: Kwo P, et al. Gastroenterology. 2017;152:164-75

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Features

- **Study Design**: Randomized, open label, parallel-group, phase 3 trial examining the safety and efficacy of a fixed-dose combination of elbasvir-grazoprevir with or without ribavirin for 12 or 16 weeks in treatment-experienced adults with GT 1, 4, or 6 HCV and previous failure of peginterferon plus ribavirin
- **Entry Criteria**:
  - 18 years or older
  - Chronic HCV Genotype 1, 4 or 6
  - HCV RNA ≥10,000 IU/mL
  - History of peginterferon plus ribavirin treatment failure
  - Patients with compensated cirrhosis accepted
  - Some patients with HIV infection accepted
- **Primary End-Point**: SVR12

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Design



Abbreviations: EBR-GZR = elbasvir-grazoprevir; RBV = ribavirin

Drug Dosing

Elbasvir-grazoprevir (50/100 mg): fixed dose combination; one pill once daily

Ribavirin (weight-based and divided bid): 800 to 1400 mg/day

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

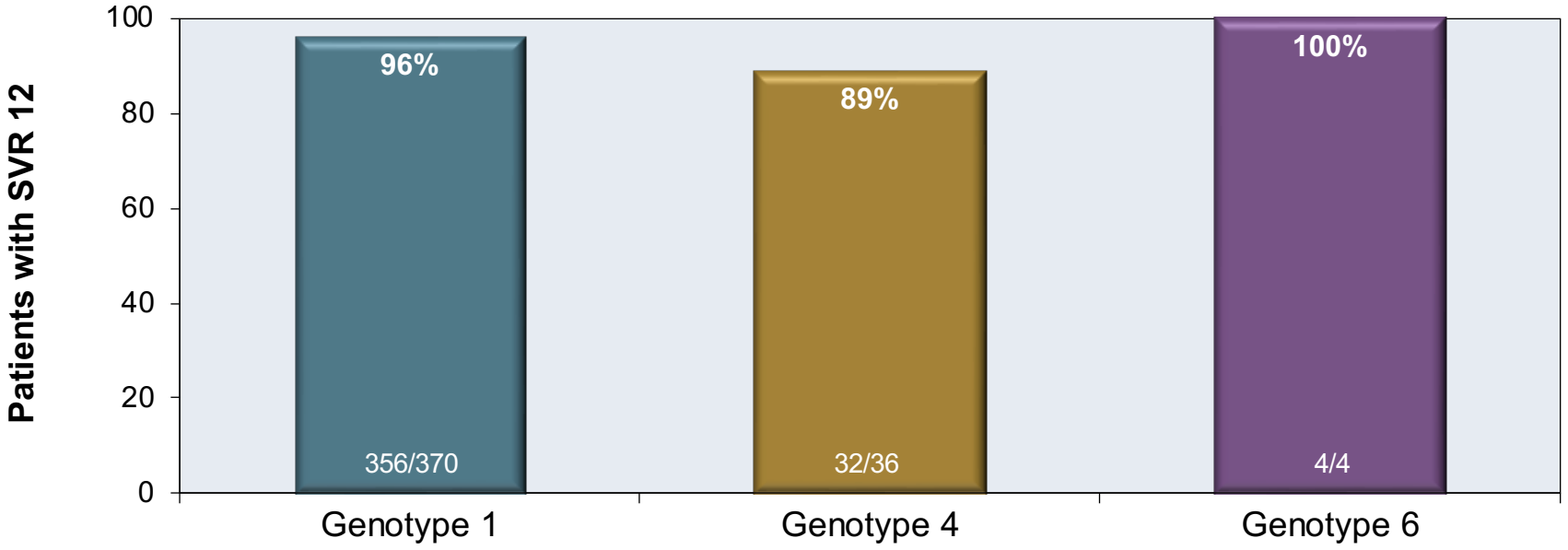
Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Baseline Characteristics

Baseline Characteristic	12-Week Treatment		16-Week Treatment	
	EBR-GZR (n = 105)	EBR-GZR + RBV (n = 104)	EBR-GZR (n = 105)	EBR-GZR + RBV (n = 106)
Age, yrs median (range)	56 (25–76)	56 (23–75)	55 (31–73)	55 (19–77)
Male sex, %	63	69	66	60
Race, n (%)				
Caucasian	66 (63)	70 (67)	72 (69)	78 (74)
African American	23 (22)	24 (23)	9 (9)	15 (14)
Asian	15 (14)	9 (9)	22 (21)	10 (9)
HCV Genotype, 1a%	61 (58)	60 (58)	48 (46)	58 (55)
HCV Genotype, 1b	34 (32)	29 (28)	48 (46)	36 (34)
HCV Genotype, 4	9 (9)	15 (14)	5 (5)	8 (8)
HCV Genotype, 6	0 (0)	0 (0)	4 (4)	2 (2)
Cirrhosis, %	37 (35)	35 (34)	38 (36)	37 (35)
HIV coinfection, %	6 (6)	5 (5)	6 (6)	4 (4)
Prior Treatment Relapse, %	35 (33)	38 (37)	38 (36)	40 (38)
Partial Treatment response, %	21 (20)	22 (21)	21 (20)	23 (22)
Prior null Treatment Response, %	49 (47)	44 (42)	46 (44)	43 (41)

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Results

C-EDGE TE: SVR 12 with Elbasvir-Grazoprevir*, by Genotype

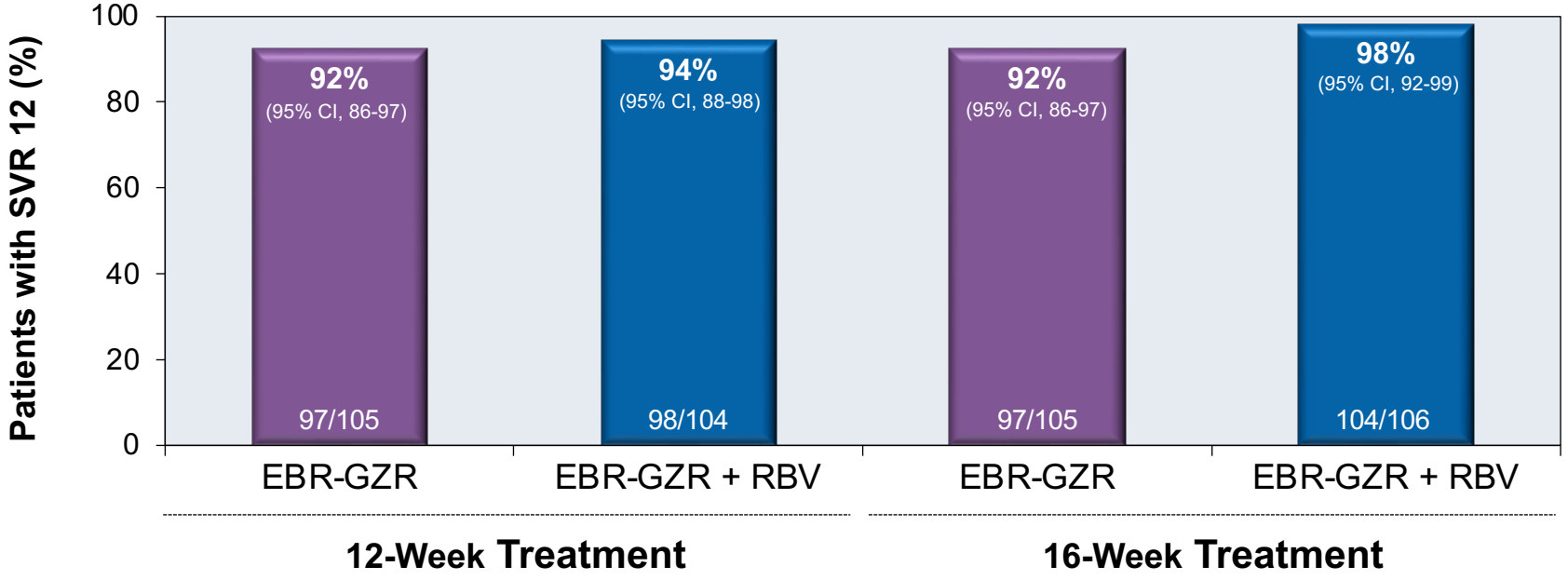


* Analysis per protocol: excluding patients who dropped out due to reasons other than virologic failure

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Results

C-EDGE TE: SVR 12* by Regimen and Treatment Duration (GT 1, 4, or 6)

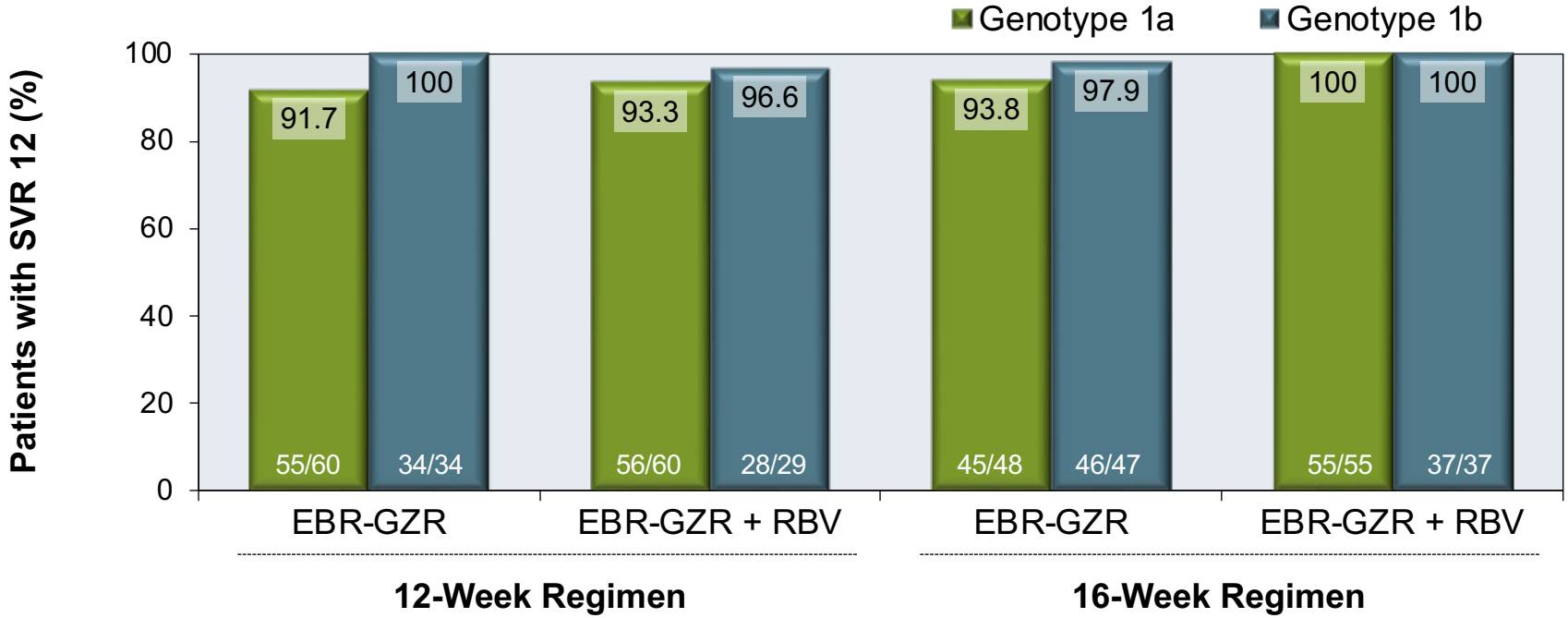


* Analysis per intent to treat

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Results

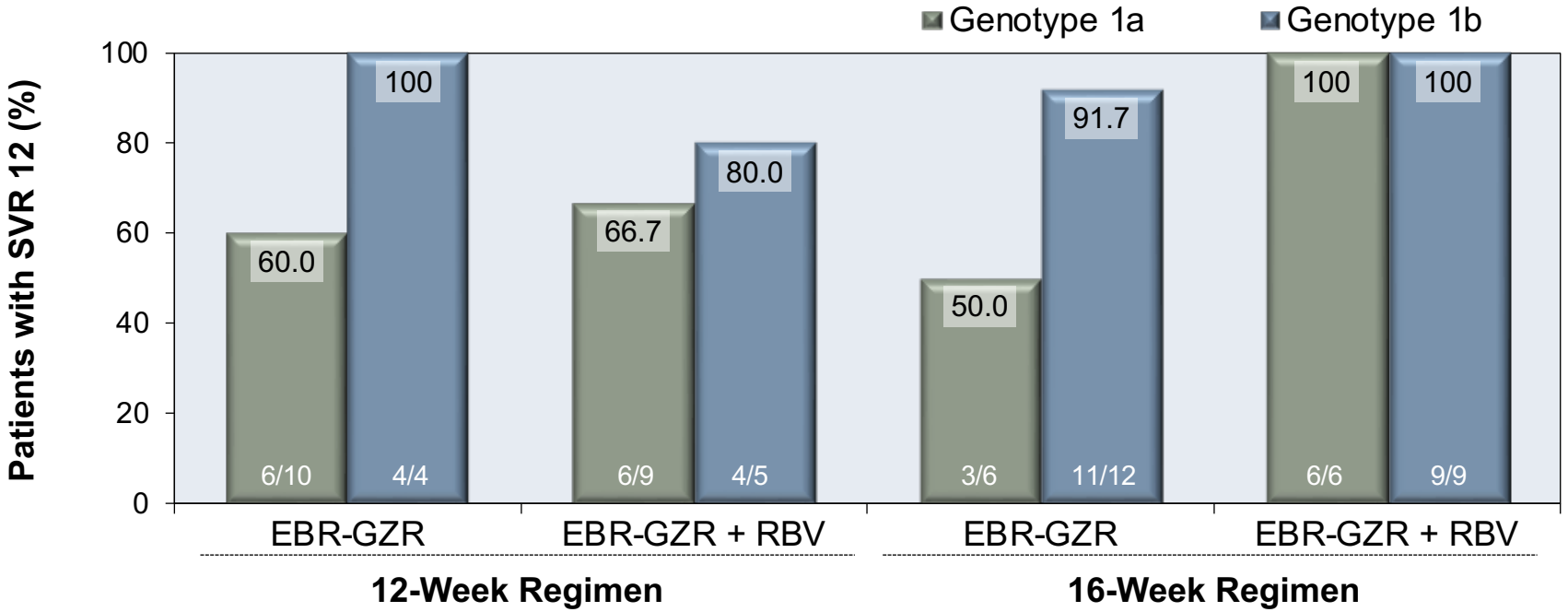
C-EDGE TE: SVR 12 by Regimen, Treatment Duration, and GT1 Subtype



Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Results

C-EDGE TE: SVR 12 in Patients with Baseline NS5A RAVs*



NS5A is by population-based sequencing (25% sensitivity threshold)

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV Genotype 1, 4, or 6
C-EDGE TE: Results

Conclusions: “The combination tablet of elbasvir and grazoprevir, with or without ribavirin, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peg-interferon and ribavirin, including patients with cirrhosis and/or a prior null response. The treatment was generally well tolerated.”

Source: Kwo P, et al. Gastroenterology. 2017;152:164-75.

Elbasvir-Grazoprevir +/- Ribavirin in HCV GT 4
Pooled Analysis

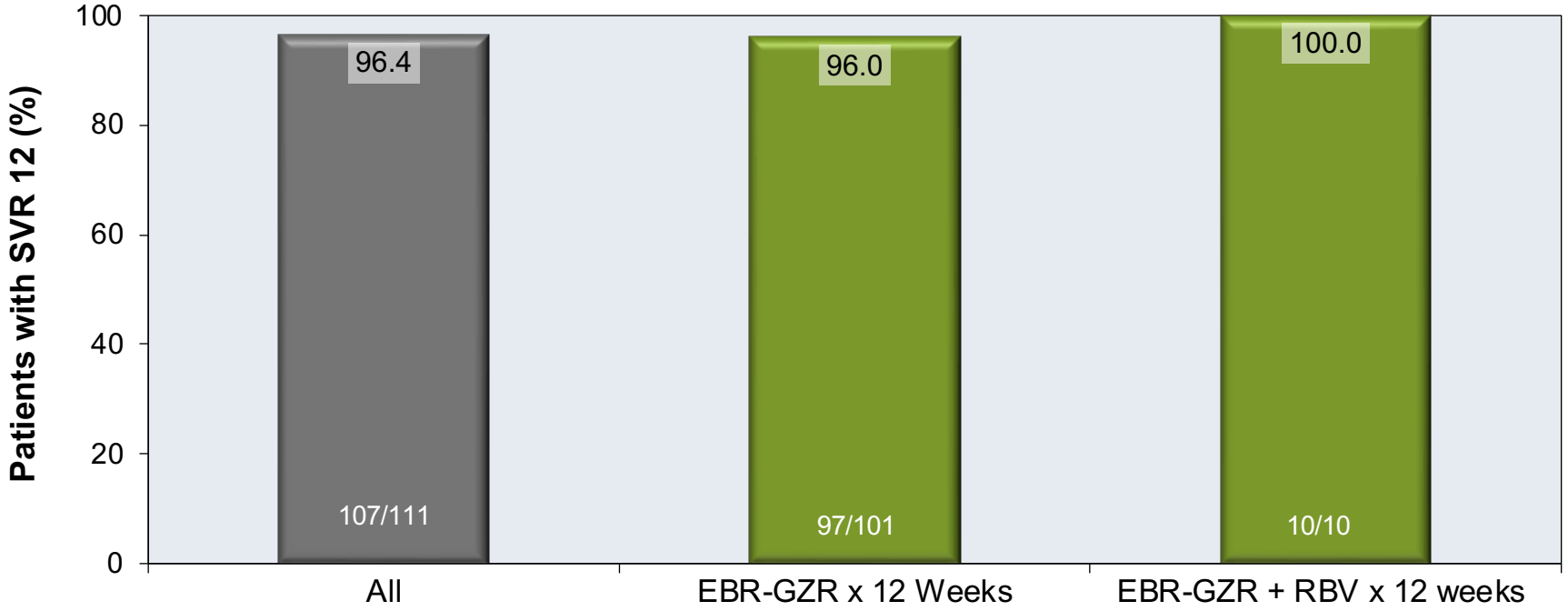
Source: Asselah T, et al. Liver Int. 2018;38:1583-91.

Elbasvir-Grazoprevir +/- RBV in HCV GT4
Pooled Analysis: Study Features

- **Design**: Pooled analysis of treatment naïve and treatment experienced adults with HCV genotype 4 who participated in phase 2 and 3 clinical trials involving treatment with elbasvir-grazoprevir for 12-16 weeks, with or without ribavirin.
- **Entry Criteria**
  - Chronic HCV genotype 4 (n = 155)
  - 18 years or older
  - Baseline HCV RNA ≥10,000 IU/mL
  - Treatment naïve & Treatment experienced (prior PEG-INF-based failure)
  - Persons with compensated cirrhosis permitted
  - Persons with HIV infection permitted
- **Primary End-Point**: SVR12

Source: Asselah T, et al. Liver Int. 2018;38:1583-91.

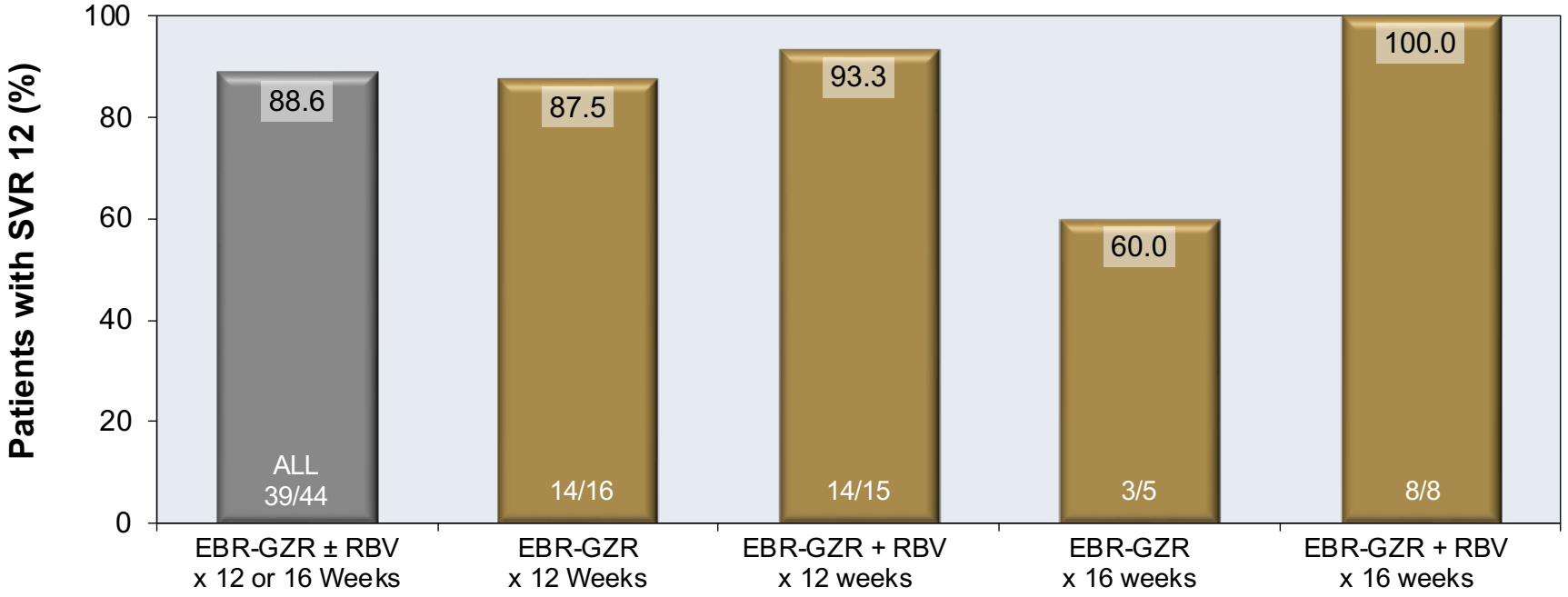
Elbasvir-Grazoprevir +/- RBV in HCV GT4
Pooled Analysis: Results in Treatment Naive



Abbreviations: EBR-GZR = elbasvir-grazoprevir; RBV = ribavirin

Source: Asselah T, et al. Liver Int. 2018;38:1583-91.

Elbasvir-Grazoprevir +/- RBV in HCV GT4
Pooled Analysis: Results in Treatment Experienced



Abbreviations: EBR-GZR = elbasvir-grazoprevir; RBV = ribavirin

Source: Asselah T, et al. Liver Int. 2018;38:1583-91.

Elbasvir-Grazoprevir +/- RBV in HCV GT4
Pooled Analysis: Conclusions

Conclusions: “The regimens of 12 weeks of elbasvir/grazoprevir without ribavirin, and 16 weeks of elbasvir/grazoprevir plus ribavirin, were efficacious in HCV GT4-infected treatment-naïve and treatment-experienced participants respectively. Baseline NS5A resistance-associated substitutions did not impact the efficacy of elbasvir/grazoprevir in GT4-infected participants.”

Source: Asselah T, et al. Liver Int. 2018;38:1583-91.

Elbasvir-Grazoprevir in HCV-HIV Coinfection

Elbasvir-Grazoprevir in HCV and HIV Coinfection, GT 1, 4, or 6

C-EDGE CO-INFECTION

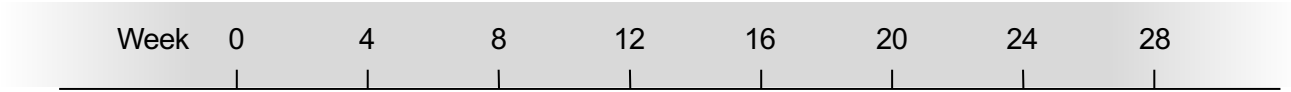
Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Study Features

- **Design**: Prospective, open-label, single-arm study examining the safety and efficacy of a fixed-dose combination of elbasvir-grazoprevir for 12 weeks in treatment-naïve patients with chronic HCV genotype 1, 4, or 6 and HIV coinfection.
- **Entry Criteria**
  - Chronic HCV Genotype 1, 4, or 6
  - Age 18 years or older
  - HCV RNA ≥10,000 IU/mL
  - No prior treatment
  - Compensated cirrhosis permitted
  - HIV infection
- **Primary End-Point**: SVR12

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Study Design



HIV-HCV Coinfected
Treatment-naïve
GT 1, 4, or 6

n = 218

Elbasvir-Grazoprevir

SVR12

Drug Dosing
Elbasvir-grazoprevir (50/100 mg): fixed dose combination; one pill once daily

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Participants

Baseline Characteristic	Elbasvir-Grazoprevir (n = 218)
Age, mean	49
Male, n (%)	183 (84%)
Race, n (%) White Black or African-American Other	 167 (77%) 38 (17%) 13 (6%)
HCV genotype, n (%) 1a 1b 4 6	 144 (66%) 44 (20%) 28 (13%) 2 (1%)
Fibrosis stage, n (%) F0-2 F3 F4	 160 (73%) 23 (11%) 35 (16%)
Mean baseline HCV RNA, $\log_{10}$ IU/ml	6.03

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Participants

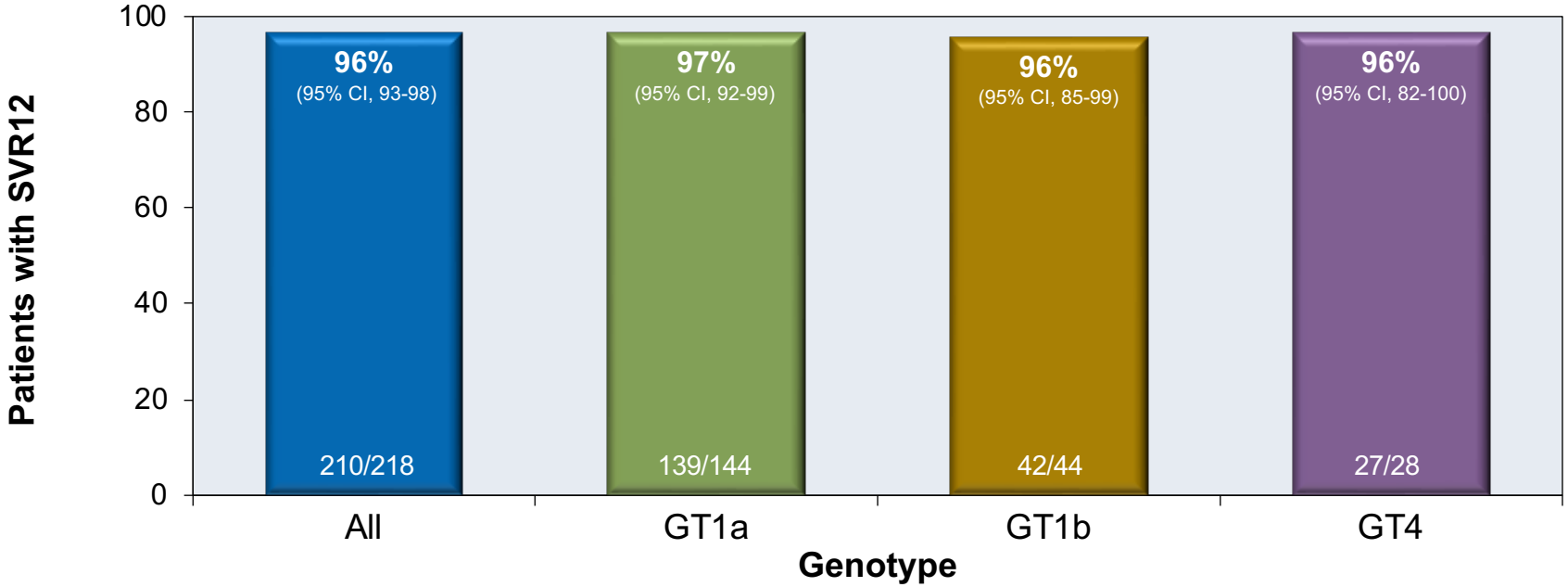
HIV Characteristics	Elbasvir-Grazoprevir (n = 218)
Median CD4 cell count, (IQR)	568 (424-766)
ART Status	
On ART with undetectable HIV RNA	211 (97%)
ART naïve	7 (3%)
ART nucleos(t)ide pair	
Abacavir-containing	47 (22%)
Tenofovir-containing	164 (75%)
None	7 (3%)
ART Third Agent	
Raltegravir	113 (52%)
Dolutegravir	59 (27%)
Rilpivirine	38 (17%)
None	8 (4%)

IQR = interquartile range; ART = antiretroviral therapy

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Results

C-EDGE CO-INFECTION: SVR12 Results by Genotype



Overall SVR12 results includes the 2 patients with GT 6, who both achieved SVR12.

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Adverse Events

Adverse Event (AE), n (%)	Elbasvir-Grazoprevir (n = 218)	
Discontinuation due to AE	0	
Serious AEs	2 (1%)	
Deaths	0	
Any AE in >5% of patients		
Fatigue	29 (13%)	
Headache	27 (12%)	
Nausea	20 (9%)	
Upper respiratory tract infection	18 (8%)	
Diarrhea	16 (7%)	
Insomnia	15 (7%)	
Grade 3 or 4 laboratory abnormality	Grade 3	Grade 4
Total bilirubin	1 (<1%)	0
ALT elevation	3 (1%)	2 (1%)
AST elevation	0	1 (<1%)
Hemoglobin	0	0

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in HCV-HIV Coinfection GT 1, 4, or 6
C-EDGE CO-INFECTION: Conclusions

Conclusions: “This HCV treatment regimen seems to be effective and well tolerated for patients co-infected with HIV with or without cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population. This regimen continues to be studied in phase 3 trials.”

Source: Rockstroh JK, et al. Lancet HIV. 2015;2:e319-27.

Elbasvir-Grazoprevir in Persons who Inject Drugs

Elbasvir-Grazoprevir in HCV GT 1,4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR

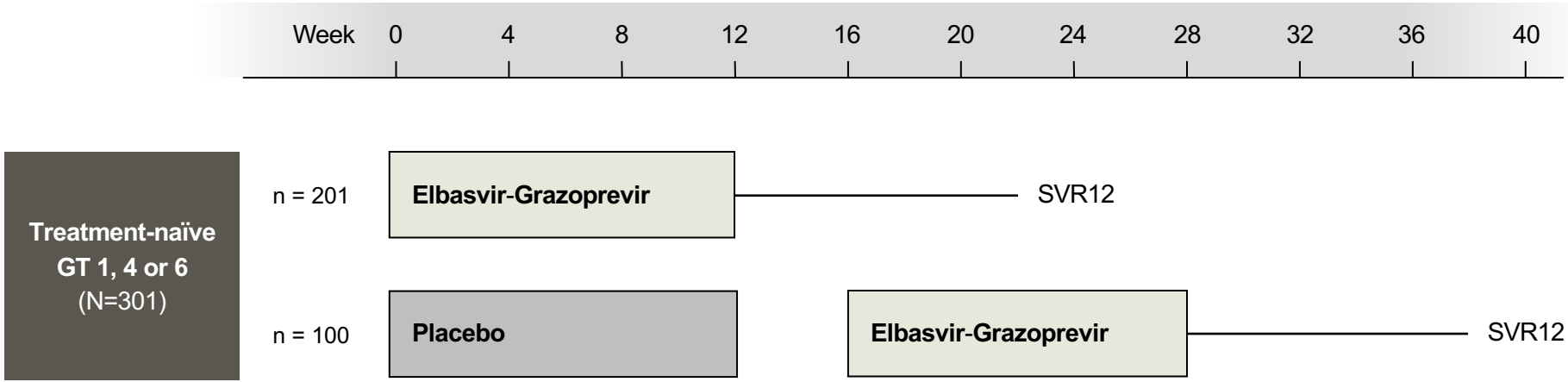
Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Study Features

- **Design**: Randomized, phase 3, placebo-controlled, double-blind, multi-site trial using a fixed-dose combination of elbasvir-grazoprevir in treatment-naïve chronic HCV genotype 1, 4, or 6 in persons who inject drugs who are receiving opiate agonist therapy
- **Entry Criteria**
  - Chronic HCV Genotype 1, 4, or 6
  - No prior treatment
  - 18 years or older
  - Opiate Agonist Therapy for ≥3 months and kept ≥ 80% of appointments
  - HCV RNA ≥10,000 IU/mL
  - Cirrhosis allowed with goal 20% of subjects with cirrhosis
  - HIV infection allowed
- **Primary End-Point**: SVR12

Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Study Features

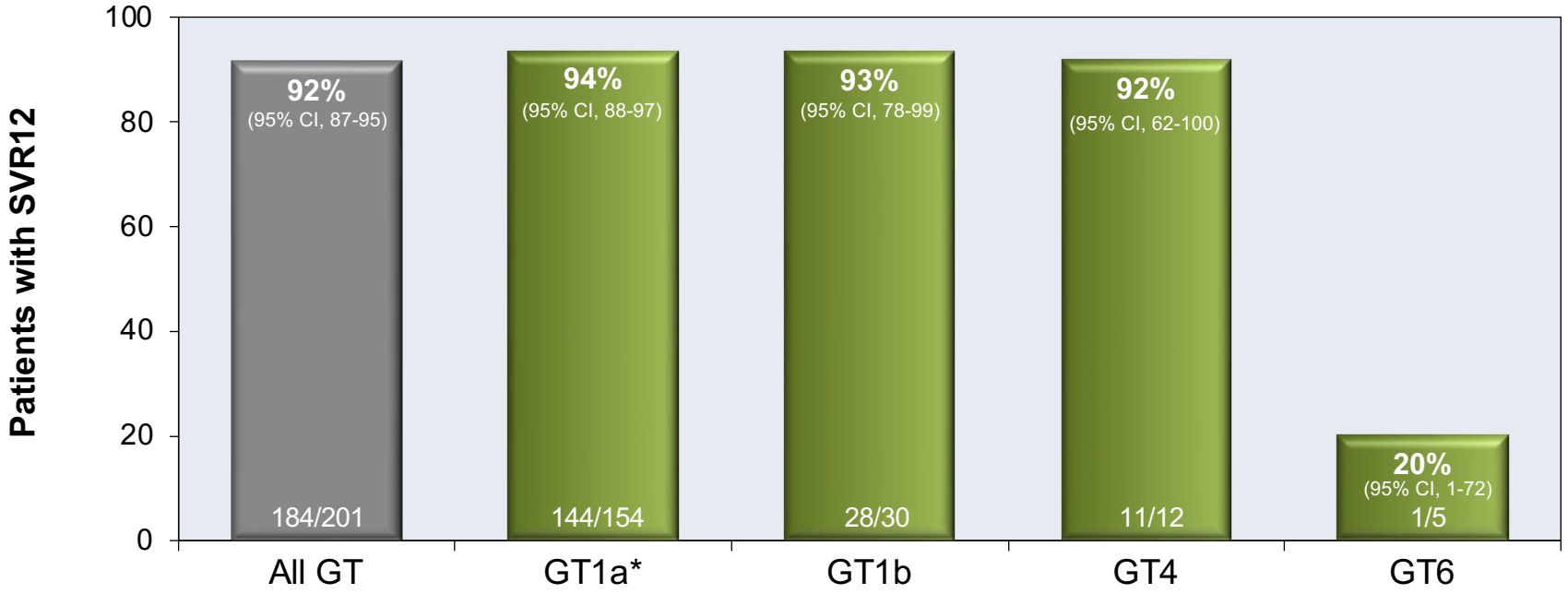


Drug Dosing
Grazoprevir-elbasvir (100/50 mg): fixed dose combination; one pill once daily

Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Results in Immediate-Treatment Group

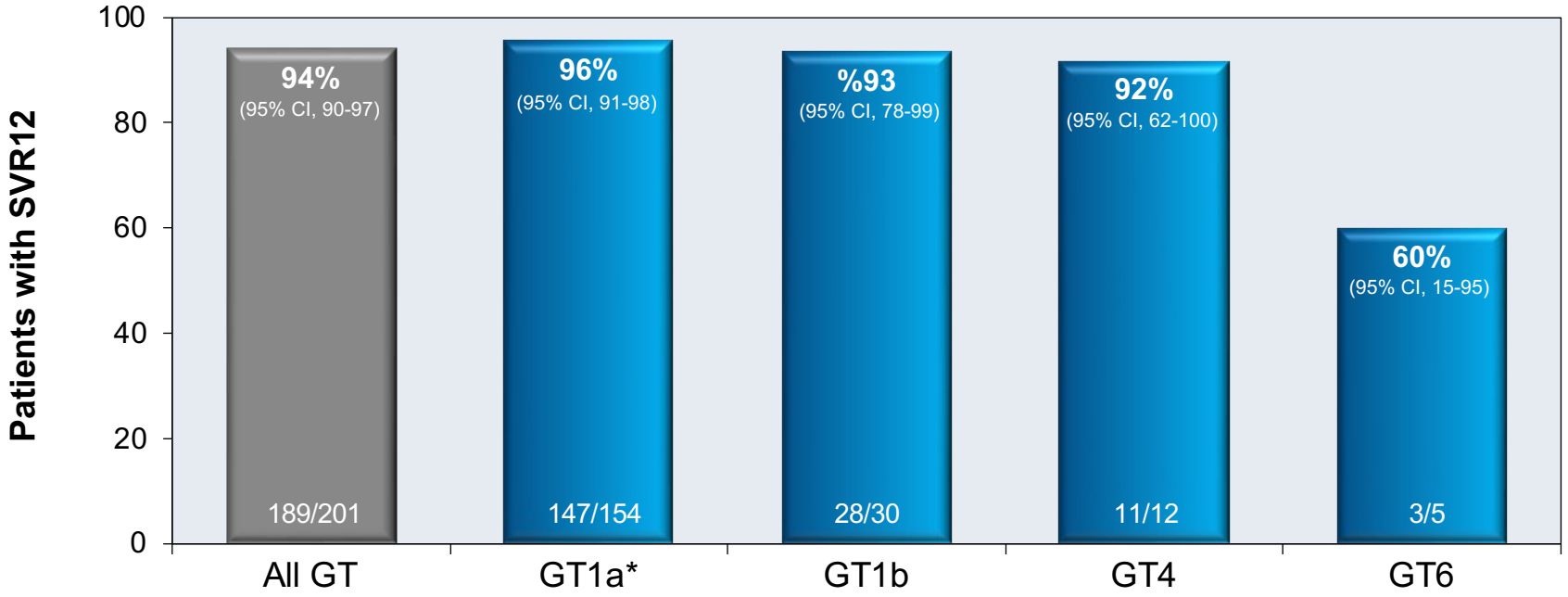
C-EDGE CO-STAR: SVR12 Results (Assumes Reinfections are Failures)



Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Results in Immediate-Treatment Group

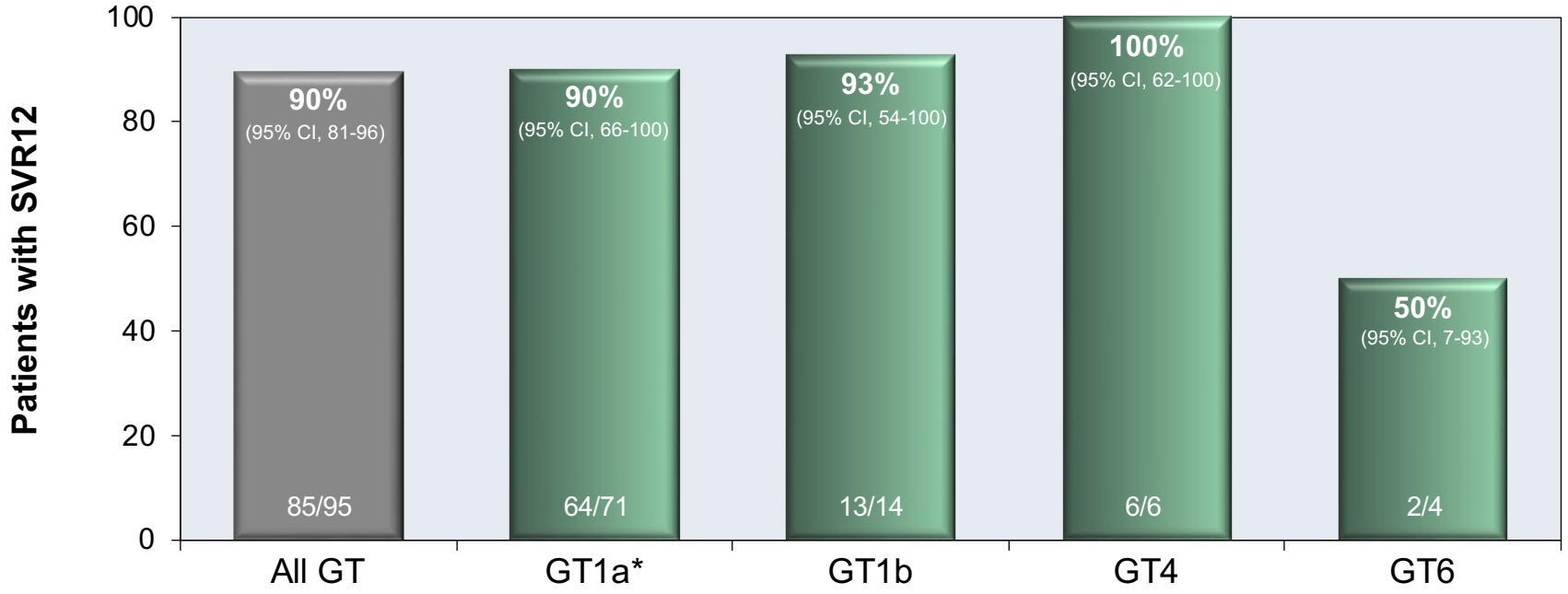
C-EDGE CO-STAR: SVR12 Results (Assumes Reinfections are Responses)



Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Results in Deferred-Treatment Group

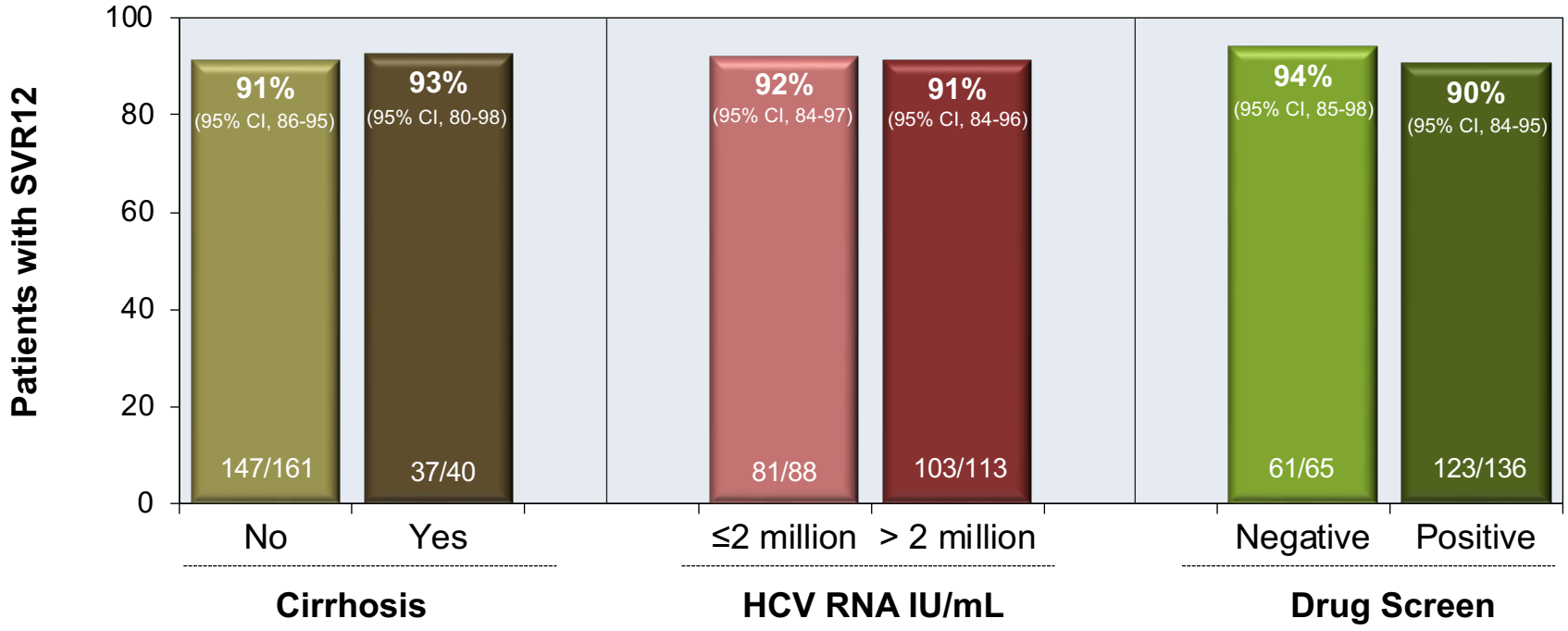
C-EDGE CO-STAR: SVR12 Results (Assumes Reinfections are Failures)



Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Results

C-EDGE CO-STAR: SVR12 Results Subgroup Analysis



Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Safety

Adverse Event (AE), n (%)	Elbasvir-Grazoprevir	
	Immediate (n = 201)	**Deferred** (Placebo) (n = 100)
Discontinuation due to AE	1 (0.5)	1 (1.0)
Serious AEs	7 (3.5)	4 (4.0)
Deaths	0	1 (1.0)
Any AE in ≥10% of patients	166 (82.6)	83 (83.0)
Fatigue	32 (15.9)	20 (20.0)
Headache	25 (12.4)	13 (13.0)
Nausea	22 (10.9)	9 (9.0)
Laboratory AEs		
Hemoglobin <8.5 g/dl	1 (0.5)	1 (1.0)
Bilirubin >2.6 times upper limit of normal	0	0
Creatinine >2.5 times baseline level	0	0

Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in HCV GT 1, 4, or 6 in PWID on Opiate Agonist Therapy
C-EDGE CO-STAR: Conclusions

Conclusions: “Patients with HCV infection who were receiving OAT and treated with elbasvir-grazoprevir had high rates of SVR12, regardless of ongoing drug use. These results support the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving Opiate Agonist Therapy (OAT).”

Source: Dore GJ, et al. Ann Intern Med. 2016;165:625-34.

Elbasvir-Grazoprevir in Persons with Renal Disease

Elbasvir + Grazoprevir in GT 1 and Chronic Renal Disease

C-SURFER

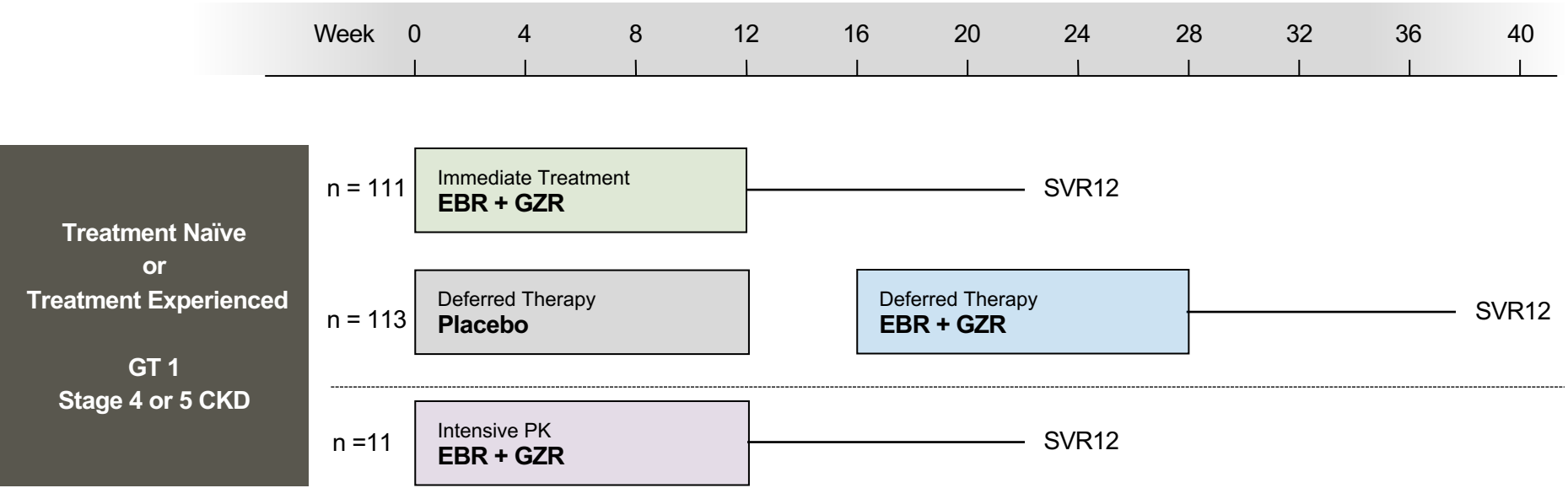
Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Features

- **Design**: Randomized, phase 3, double-blind trial examining the safety and efficacy of elbasvir plus grazoprevir for 12 weeks in treatment-naïve or treatment-experienced patients genotype 1 chronic HCV and stage 4 or 5 chronic renal disease, including patients on hemodialysis.
- **Setting**: 68 international sites
- **Entry Criteria**
  - Chronic HCV genotype 1
  - Chronic kidney disease (Stage 4 or 5) +/- hemodialysis
  - Age 18 years or older
  - Treatment naïve or treatment-experienced
  - Cirrhosis allowed
- **Primary End-Point**: SVR12

Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Study Design



Drug Dosing
Elbasvir 50 mg once daily and Grazoprevir 100 mg once daily; given as separate medications in Immediate treatment and Intensive PK arms; given as fixed dose combination in Deferred arm

Source: Roth D, et al. Lancet 2015;386:1537-45.

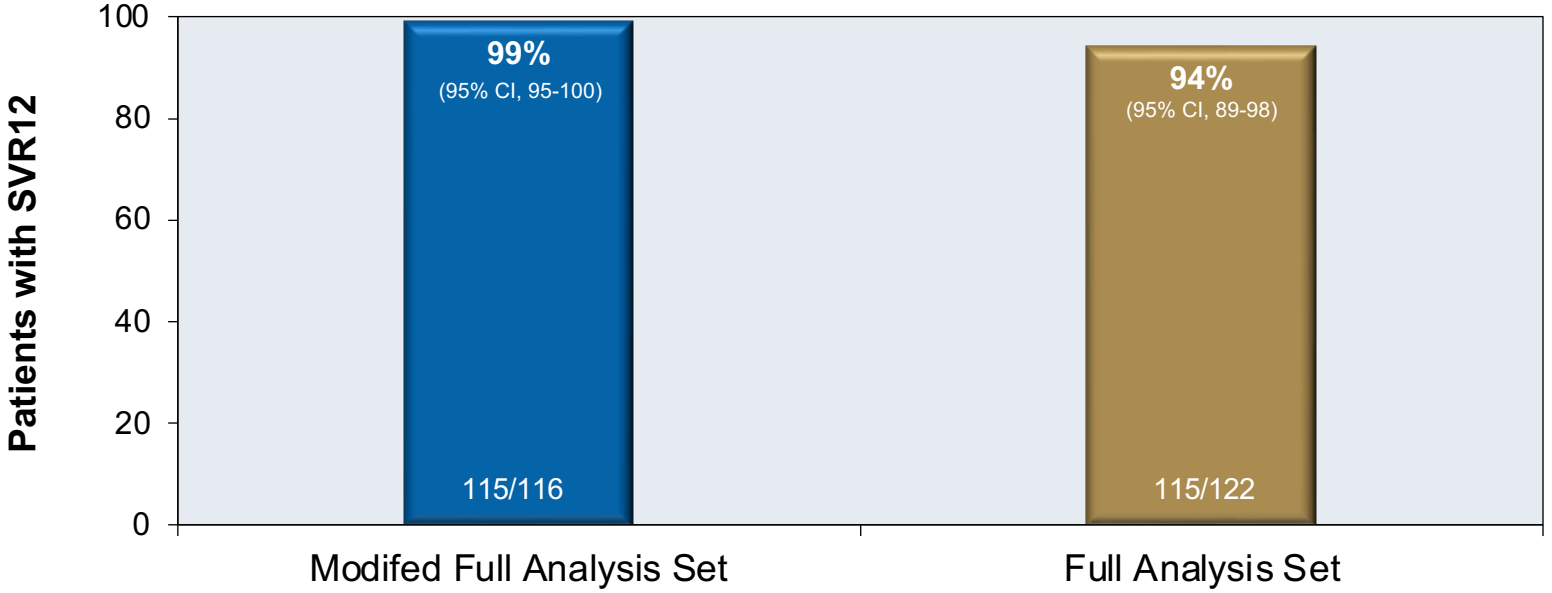
Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Participants

Baseline Characteristic	EBR + GZR *Immediate* (n = 111)	EBR + GZR *Deferred* (n = 113)	EBR + GZR *PK* (n = 11)	Total (n = 235)
Mean age, years (SD)	56.5 (9.1)	55.2 (10.1)	58.2 (6.8)	56 (9.5)
Male sex, %	73	71	100	73
Race, %				
White	50	43	54	47
Black	45	47	45	46
Asian	5	8	0	6
HCV Genotype, %				
1a	48	52	91	52
1b	52	47	9	48
1 other	0	1	0	0
Cirrhosis, %	6	6	0	6
Treatment-naïve, %	82	78	91	80
Diabetes, %	34	32	55	34
Kidney disease severity				
Stage 4, %	16	20	36	19
Stage 5, %	84	80	64	81
On dialysis, %	78	77	55	76

Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Results

C-SURFER: Elbasvir + Grazoprevir SVR12 Results



Modified analysis excluded patients who did not receive ≥1 dose of drug or who died or discontinued early for reasons unrelated to HCV treatment.

Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Safety

Adverse Event (AE), n (%)	Elbasvir + Grazoprevir	
	Immediate (n = 111)	**Deferred** (Placebo) (n = 113)
Discontinuation due to AE	0	5 (4.4)
Serious AEs	16 (14.4)	19 (16.8)
Deaths	1 (0.8)	3 (2.7)
Any AE in ≥10% of patients	84 (75.7)	95 (84.1)
Headache	19 (17.1)	19 (16.8)
Nausea	17 (15.3)	18 (15.9)
Fatigue	11 (9.9)	17 (15.9)
Insomnia	7 (6.3)	12 (10.6)
Dizziness	6 (5.4)	18 (15.9)
Diarrhea	6 (5.4)	15 (13.3)
Laboratory AEs		
Hemoglobin <8.5 g/dl	5 (4.5)	5 (4.4)
ALT 1.1-2.5 x baseline	2 (1.8)	36 (31.9)
Creatinine[§] >2.5 x baseline	1 (1.2)	0

[§]Among patients not on dialysis at baseline.

Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir + Grazoprevir in HCV GT1 and Renal Disease
C-SURFER Study: Conclusions

Conclusions: “Once-daily grazoprevir and elbasvir for 12 weeks had a low rate of adverse events and was effective in patients infected with HCV genotype 1 and stage 4-5 chronic kidney disease.”

Source: Roth D, et al. Lancet 2015;386:1537-45.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis
Integrated Analysis

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Study Features

- **Design**: Integrated analysis of data from six phase 2/3 trials of elbasvir-grazoprevir with or without ribavirin in patients with compensated cirrhosis: C-SURFER, C-EDGE COINFECTION, C-EDGE (NAÏVE & EXPERIENCED), C-WORTHY and C-SALVAGE
- **Entry Criteria**
  - Chronic HCV Genotype 1, 4, or 6
  - Child Pugh class A compensated cirrhosis
  - No prior treatment or treatment with peginterferon + ribavirin +/- 1st generation protease inhibitor (boceprevir, telaprevir, simeprevir)
  - 18 years or older
  - HCV RNA ≥10,000 IU/mL
  - HIV infection allowed
- **Primary End-Point**: SVR12

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Baseline Characteristics

Baseline Characteristic, n (%)	Elbasvir-Grazoprevir	
	Treatment Naïve (n = 169)	Treatment Experienced (n = 233)
Male	113 (67)	151 (65)
Age, y, mean (range)	56 (32-82)	57 (19-76)
Race		
White	131 (77.5)	193 (83)
Black	16 (9.5)	21 (9)
Asian	17 (10)	19 (8)
Other	5 (3)	0
Latinx	11 (6.5)	21 (9)
HCV genotype 1a	96 (57)	123 (53)
HCV genotype 1b or other	67 (41)	90 (39)
HCV genotype 4	6 (4)	17 (7)
HCV genotype 6	0	3 (1)
IL28B CC genotype	63 (37)	32 (14)
BMI ≥30 kg/m^2	34 (20)	68 (29)

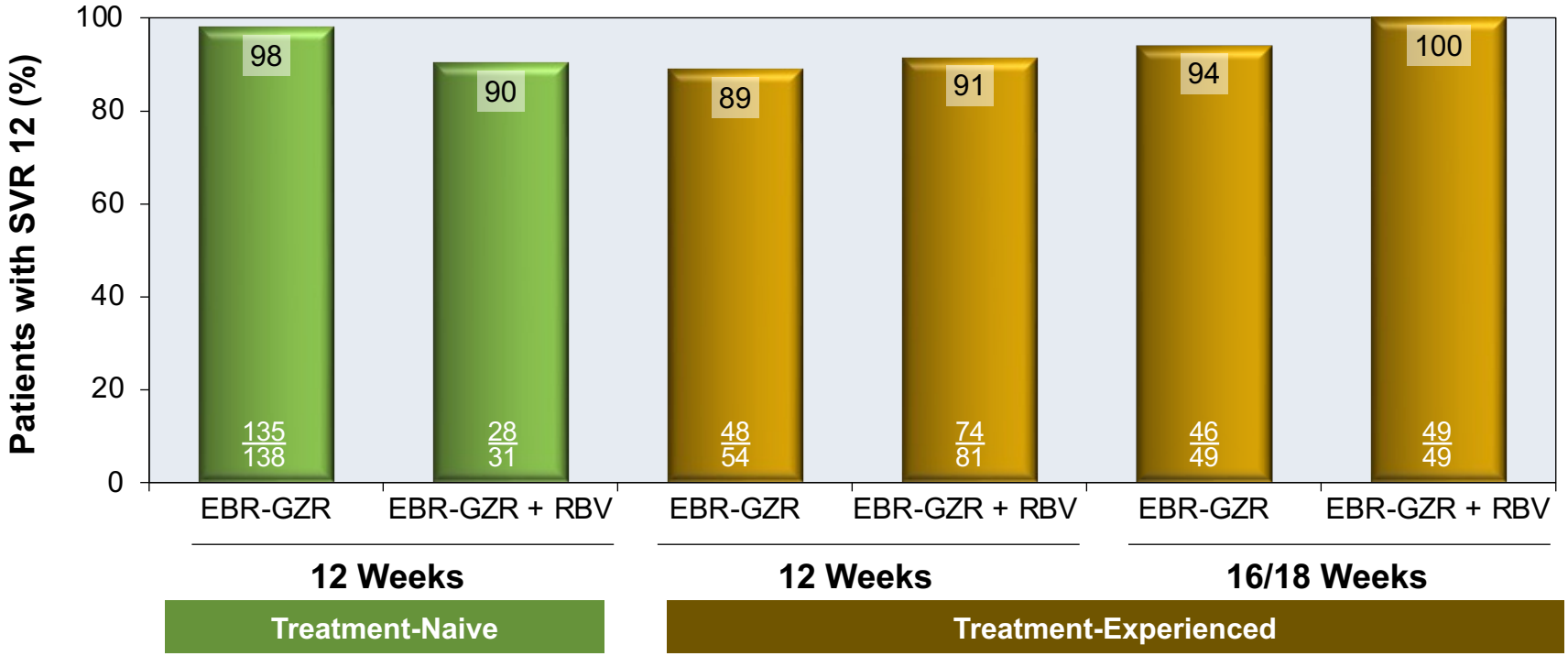
Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Baseline Characteristics

Baseline Characteristic, n (%)	Elbasvir-Grazoprevir	
	Treatment Naïve (n = 169)	Treatment Experienced (n = 233)
HIV coinfection	35 (21)	5 (2)
Chronic kidney disease, stage 4 or 5	4 (2.4)	3 (1.3)
Prior treatment response		
Null	NA	120 (51.5)
Relapse	NA	59 (25)
Prior DAA	NA	34 (14.6)
Platelet count <100 x 10^3/μL	40 (24)	61 (26)
Albumin <3 g/dL	0	1 (0.4)
Cirrhosis determination method		
Biopsy	43 (25)	72 (31)
ALT-platelet ratio index + FibroTest	12 (7)	17 (7)
FibroScan	114 (67.5)	144 (62)
12.6 – 15 kPa	33 (29)	35 (24)
15.1 – 20 kPa	40 (35)	33 (23)
20.1-25 kPa	10 (9)	14 (10)
>25 kPa	31 (27)	62 (43)

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

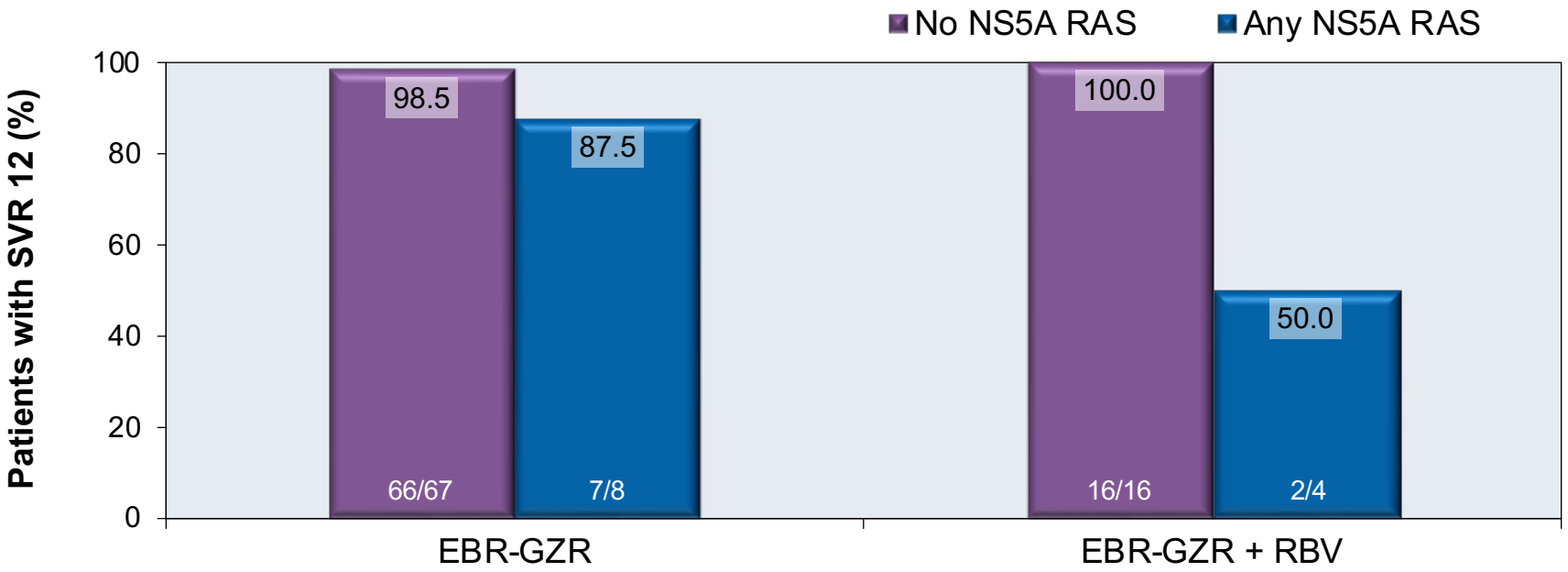
Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Results



Abbreviations: EBR-GZR = elbasvir-grazoprevir; SOF = sofosbuvir; RBV = ribavirin

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Treatment-Naive

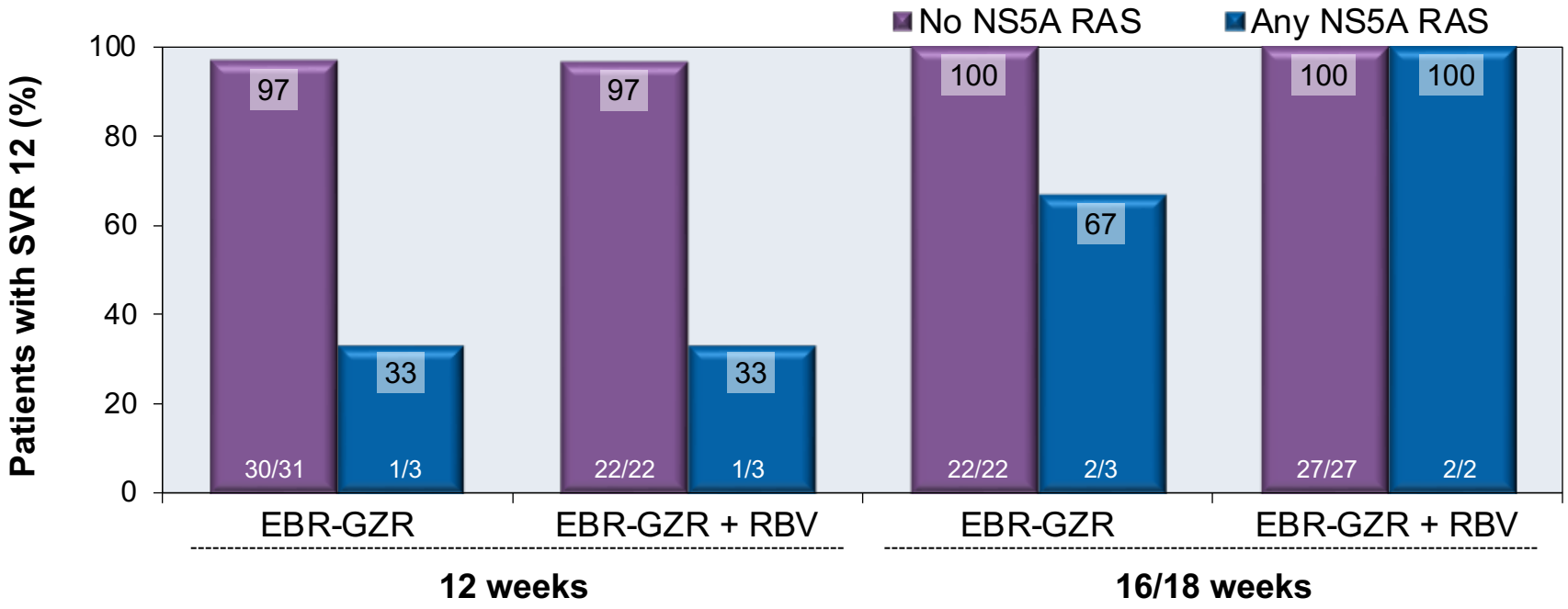


Abbreviations: RA = resistance-associated variant; EBR-GZR = elbasvir-grazoprevir; RBV = ribavirin

Note: RAS testing was via population-based sequencing with 25% threshold.

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Treatment-Experienced



Abbreviations: RA = resistance-associated variant; EBR-GZR = elbasvir-grazoprevir; RBV = ribavirin

Note: RAS testing was via population-based sequencing with 25% threshold.

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Elbasvir-Grazoprevir in Persons with Compensated Cirrhosis Integrated Analysis: Conclusions

Conclusions: “In an analysis of data from 6 clinical trials, rates of SVR12 ranged from 89% to 100% in patients with HCV genotype 1, 4, or 6 infections and compensated cirrhosis treated with elbasvir/grazoprevir, with or without ribavirin. Addition of ribavirin to a 12-week regimen of elbasvir/grazoprevir had little effect on the proportion of treatment-naïve or treatment-experienced patients who achieved an SVR12.”

Source: Jacobson IM, et al. Gastroenterology. 2017;152:1372-82.e2.

Acknowledgments

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HEPATITIS B ONLINE

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