Current Medications for Hepatitis C

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Dushyantha Jayaweera MD, MRCOG(UK) FACP

Associate Vice Provost for Human Subject Research

Professor of Clinical Medicine

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AASLD/IDSA Guidance on HCV Management

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Treatment Benefits All Pts

- AASLD/IDSA guidance emphasizes the potential benefits of and recommends treatment for all patients with HCV infection

- Urgent treatment initiation recommended for:
  - Advanced fibrosis (Metavir F3)
  - Compensated cirrhosis (Metavir F4)
  - Liver transplantation
  - Severe extrahepatic HCV

- Reduced HCV transmission expected with treatment of:
  - Women wishing to become pregnant
  - Long-term hemodialysis pts
  - MSM with high-risk sexual practices
  - Injection drug users
  - Incarcerated persons

Recommended Regimens for GT1

- Options listed alphabetically, not by order of preference
- LDV/SOF (QD) ± RBV for 12-24 wks
- OMV/PTV/RTV (QD) + DSV (BID) ± RBV for 12-24 wks
  - Not recommended for pts with prior PI failure
- SMV (QD) + SOF (QD) ± RBV for 12-24 wks
  - Not recommended for pts with prior SOF or PI failure
- Regimens no longer recommended for GT1
  - SOF + RBV, pegIFN, boceprevir, telaprevir

Recommended Regimens for Treatment-Naive GT1 HCV Pts

Subtype	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
GT1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
GT1a	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
GT1b	SMV + SOF	12	SMV + SOF	24

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider's discretion but should be done with caution.

Recommended Regimens for Treatment-Experienced GT1 HCV Pts

Population	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
Prior PegIFN/RBV				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12
▪ GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
▪ GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
▪ GT1a or 1b	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
Prior SOF				
▪ GT1a or 1b	Defer therapy*		LDV/SOF ± RBV	24
Prior PI				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12

*Based on limited available data, pts without advanced fibrosis and without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider clinical trial.

FDA-Approved All-Oral Regimens for GT1

Population	Regimen	Duration
GT1, TN or TE, noncirrhotic	SMV + SOF[1]	12 wks
GT1, TN or TE, cirrhotic	SMV + SOF[1]	24 wks
GT1 interferon ineligible	SOF + RBV[2]	24 wks*
GT1, TN	SOF/LDV[3]	12 wks†
GT1, TE, noncirrhotic	SOF/LDV[3]	12 wks
GT1, TE, cirrhotic	SOF/LDV[3]	24 wks
GT1a, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV + RBV[4]	12 wks
GT1a, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV[4]	24 wks‡
GT1b, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV[4]	12 wks
GT1b, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV[4]	12 wks

*Not recommended per AASLD/IDSA guidance.
†8-wk course can be considered in pts without cirrhosis with pretreatment HCV RNA < 6 million IU/mL.
‡12-wk course may be considered for some patients based on previous treatment history.

1. Simeprevir [package insert]. 2. Sofosbuvir [package insert]. 3. Sofosbuvir/ledipasvir [package insert].
4. Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

All-Oral Regimens for Other Populations

Population	Regimen	Duration
GT2	SOF + RBV[1]	12 wks
GT3	SOF + RBV[1]	24 wks
GT1/2/3/4 HCC pre-OLT	SOF + RBV[1]	48 wks*
GT1, post-OLT (Metavir ≤ 2)	OMV/PTV/RTV + DSV + RBV[2]	24 wks
GT1/4 decompensated cirrhosis (CTP B or C)	SOF/LDV + RBV†[3]	12 wks‡
GT2/3 decompensated cirrhosis (CTP B or C)	SOF + RBV†[3]	Up to 48 wks

*Up to 48 wks or until transplantation, whichever occurs first. †Not FDA approved but recommended in AASLD/IDSA guidance. ‡24 wks of SOF/LDV if anemia or RBV intolerance; 24 wks of SOF/LDV + RBV (600 mg/day with increasing dose if tolerated) if prior SOF failure.

1. Sofosbuvir [package insert]. 2. Ombitasvir/paritaprevir/ritonavir plus dasabuvir [package insert].
3. AASLD/IDSA HCV Guidelines. Accessed January 5, 2015.

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Recommended Regimens for GT4

- Recognizing that data are limited, AASLD/IDSA guidance makes these recommendations
  - LDV/SOF for 12 wks
  - OMV/PTV/RTV + RBV for 12 wks
  - SOF + RBV for 24 wks
    - Recommended in treatment-experienced and as alternative for treatment-naive pts: SOF + RBV + peg IFN for 12 wks
    - Alternative for treatment-naive pts: SOF + SMV ± RBV for 12 weeks

Recommended for HCV genotype 2

- Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks. Rating: Class I, Level A

Recommended for HCV Genotype 3

- Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection. Rating: Class I, Level B

- Alternative regimens for treatment-naïve: Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3. Rating: Class IIa, Level A

Treatment of HCV GT 5 and 6

Recommended

- Sofosbuvir (400 mg/d) and weight-based RBV plus weekly PEG for 12 weeks. Rating: Class IIa, Level B

Alternate

- Daily weight-based RBV plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6. Rating: Class IIb, Level A

Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected pts
- Consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - Do not interrupt antiretroviral therapy
  - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org
- Do not use OMV/PTV/RTV ± DSV in coinfected pts not taking antiretroviral therapy

Guidance for Renal Impairment

- If CrCl > 30 mL/min, no dosage adjustment needed with
  - LDV/SOF
  - OMV/PTV/RTV + DSV
  - SMV
  - SOF
- If CrCl < 30 mL/min, consult with expert—limited safety and efficacy data available

Guidance for Decompensated Cirrhotics

- Refer to experienced HCV practitioner (ideally liver transplant center)
- Avoid IFN, TVR, BOC, SMV, OMV/PTV/RTV + DSV
- GT1/4 HCV infection
  - LDV/SOF + RBV* for 12 wks
    - Consider 24 wks for prior SOF failure
  - LDV/SOF for 24 wks in pts with anemia or RBV intolerance
- GT2/3 HCV infection
  - SOF + RBV† for up to 48 wks

*Initial dose of 600 mg daily, increased as tolerated.
†1000-1200 mg daily based on weight, with consideration for pt's CrCl and hemoglobin

Guidance for Recurrent HCV Post Liver Transplantation

- For pts with GT1 infection
  - Recommended
    - LDV/SOF + RBV for 12 wks
  - Alternative
    - SOF + SMV ± RBV for 12 wks
    - For F0-F2: OMV/PTV/RTV + DSV + RBV for 24 wks
    - For treatment naive: LDV/SOF for 24 wks

Management of Acute HCV Infection

- If treatment delay acceptable, monitor for spontaneous clearance for 6-12 mos
  - Monitor HCV RNA every 4-8 wks
- If treatment initiated during acute infection phase
  - Monitor for spontaneous clearance at least 12-16 wks before treatment
  - Recommended regimens are the same as for chronic HCV infection

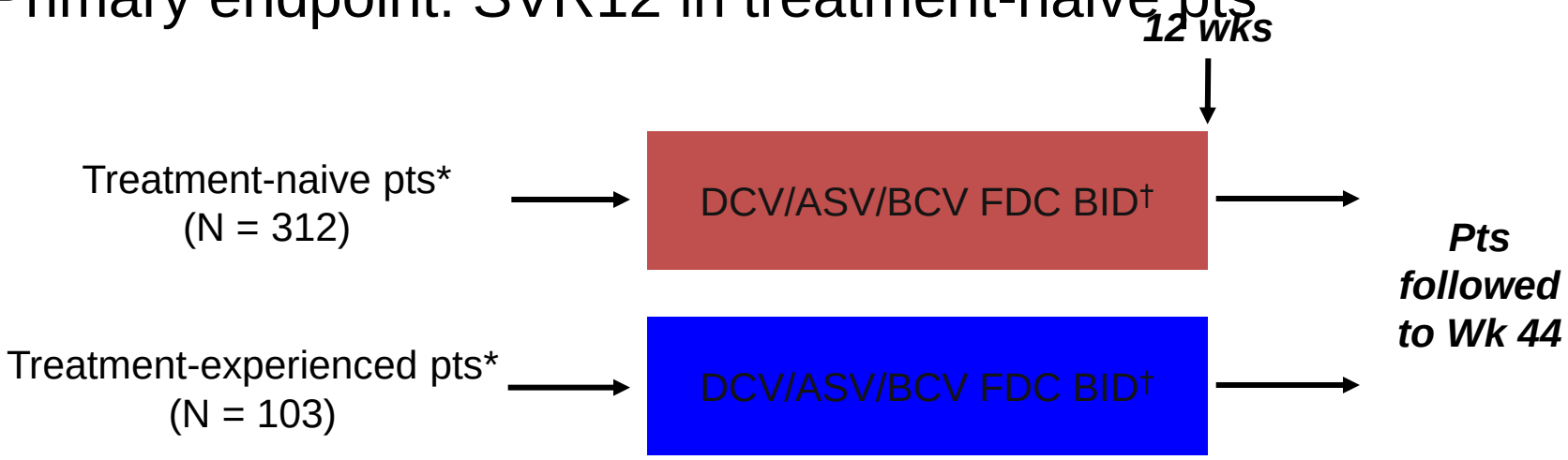
Key Monitoring Guidance

- Before treatment
  - Degree of hepatic fibrosis by noninvasive testing or by biopsy
  - Potential drug–drug interactions (hep-druginteractions.org)
- Before and during treatment
  - HCV RNA before treatment and at Wk 4
    - If detectable at Wk 4, assess again at Wk 6 only
  - ALT before treatment and at Wk 4
    - If elevated at Wk 4, assess again at Wk 6 and Wk 8
- After treatment
  - If pretreatment Metavir ≥ F3, ultrasound for HCC every 6 mos

New Agents

UNITY-1: Fixed-Dose Daclatasvir/ Asunaprevir/Beclabuvir in Noncirrhotic GT1

- Nonrandomized, open-label phase III trial
- Primary endpoint: SVR12 in treatment-naive pts



*73% GT1a HCV, 27% GT1b HCV.

†DCV 30 mg/ASV 200 mg/BCV 75 mg administered BID as FDC tablet.

Poordad F, et al. AASLD 2014. Abstract LB-7.

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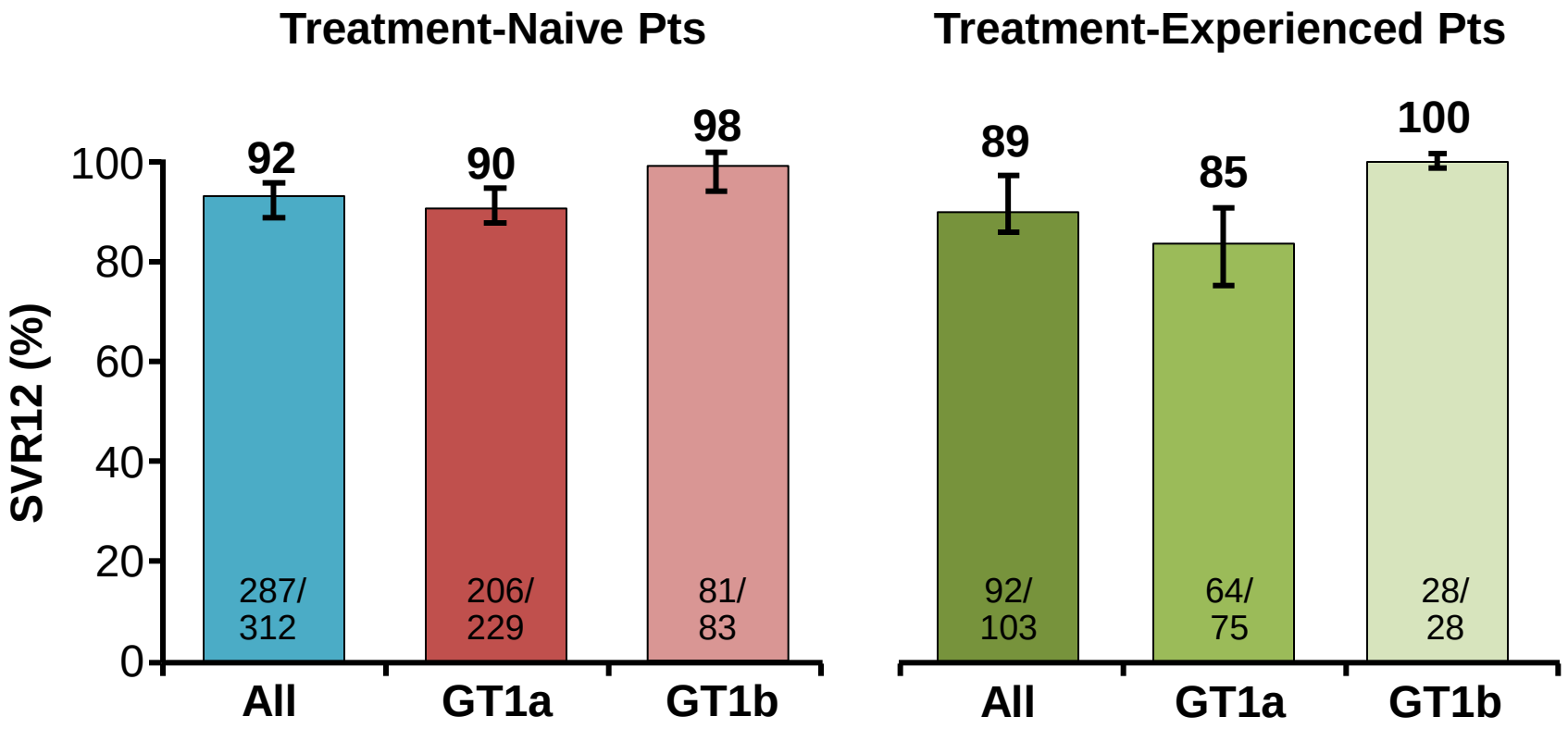
UNITY-1: Efficacy of DCV/ASV/BCV in Noncirrhotic GT1 by Treatment Experience



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UNITY-1: Safety and Tolerability of DCV/ASV/BCV in Noncirrhotic GT1 Patients

Parameter, %	All Pts Receiving DCV/ASV/BCV (N = 415)
Death	0.2
Serious AEs	2
AEs leading to d/c	0.7
Any AE	79
AEs in ≥ 10% of pts	
▪ Headache	26
▪ Fatigue	17
▪ Diarrhea	14
▪ Nausea	13
Grade 3/4 laboratory abnormalities (selected)	
▪ ALT > 5 x ULN	5
▪ Total lipase > 3 x ULN	4

- Treatment d/c due to ALT elevation occurred in 2 pts

Poordad F, et al. AASLD 2014. Abstract LB-7.

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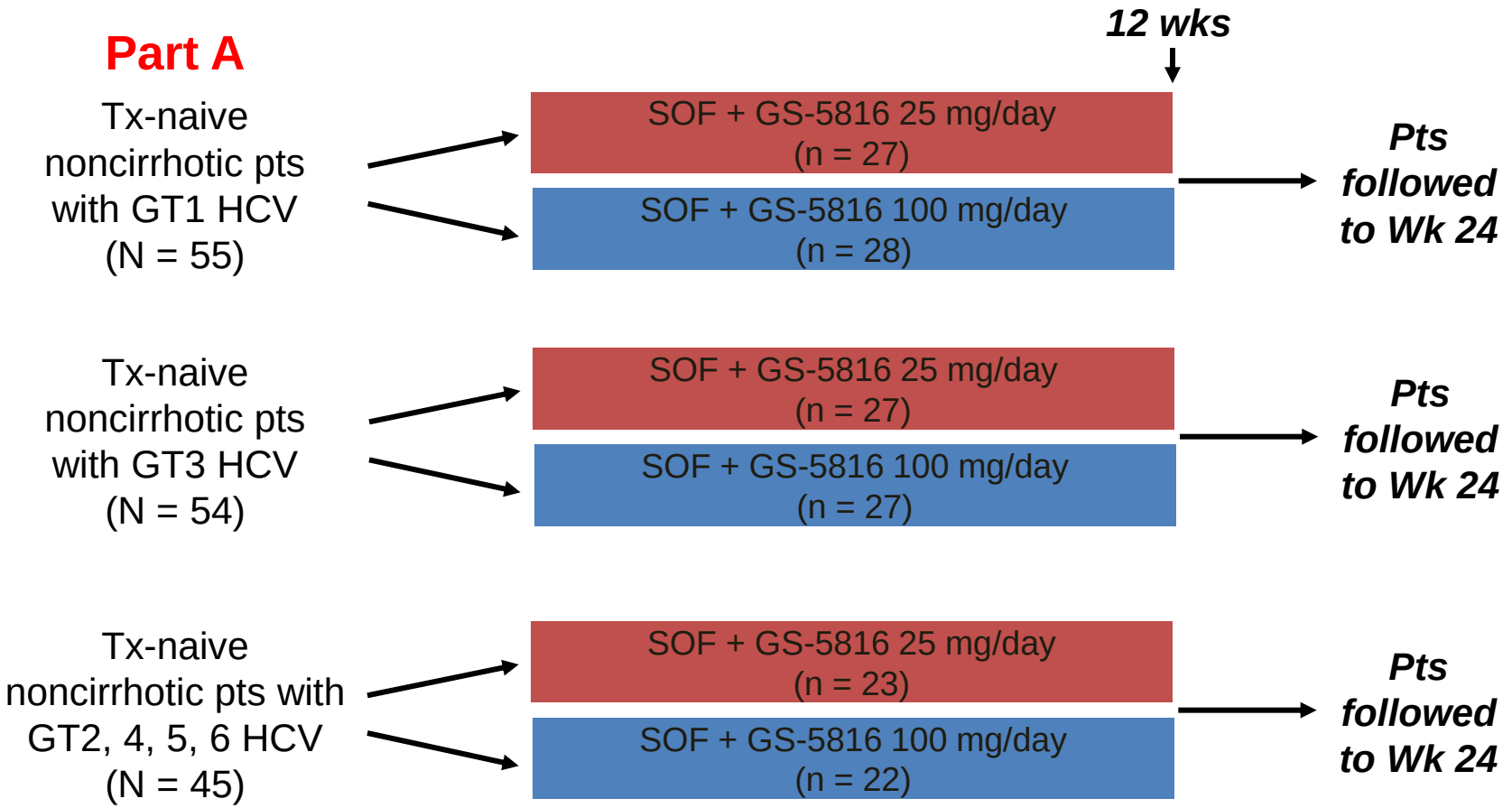
SOF + GS-5816 ± RBV x 8 or 12 Wks in Tx-Naive Noncirrhotic Pts With GT1-6 HCV



Tran TT, et al. AASLD 2014. Abstract 80.

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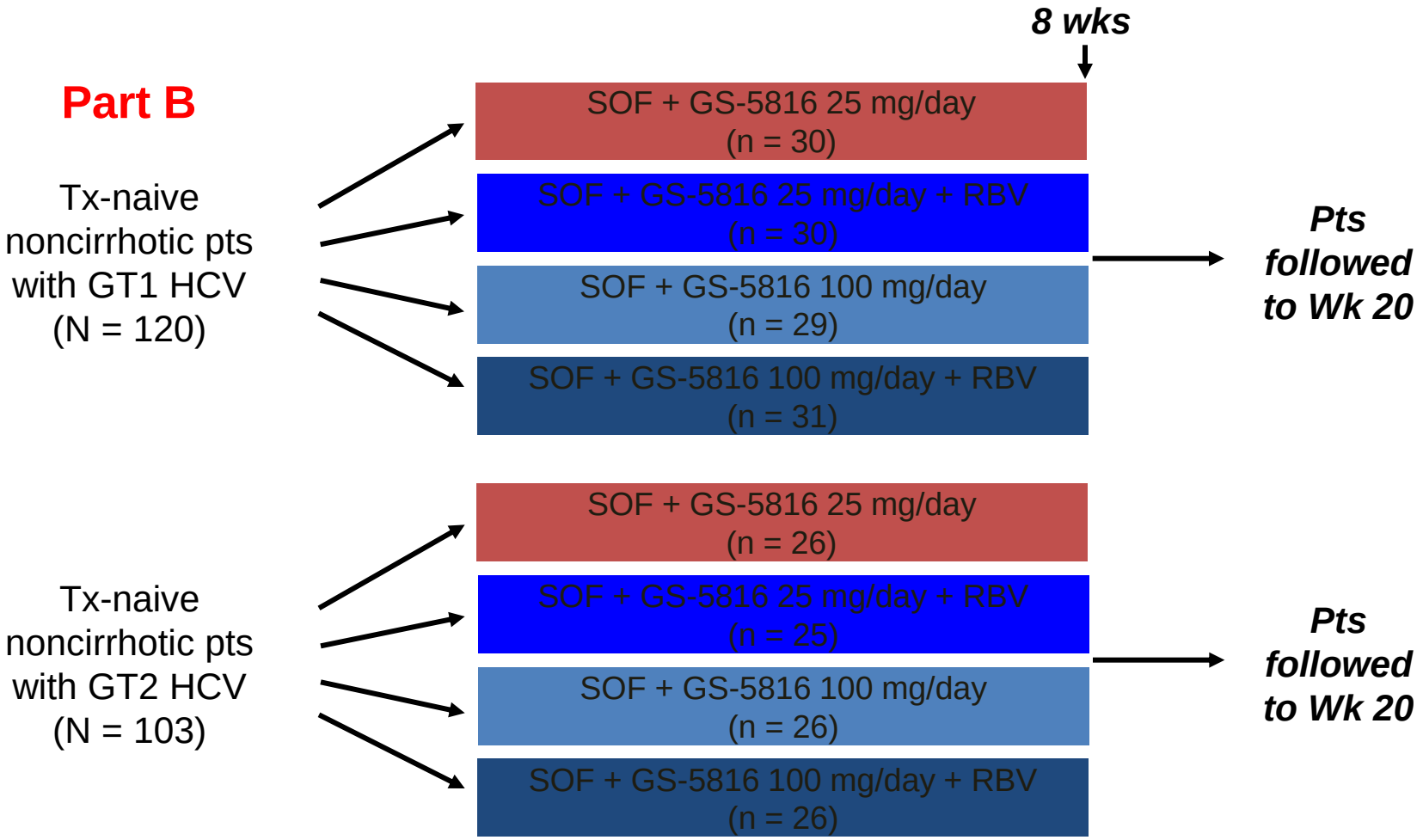
SOF + GS-5816 ± RBV x 8 or 12 Wks in Tx-Naive Noncirrhotic Pts With GT1-6 HCV



Tran TT, et al. AASLD 2014. Abstract 80.

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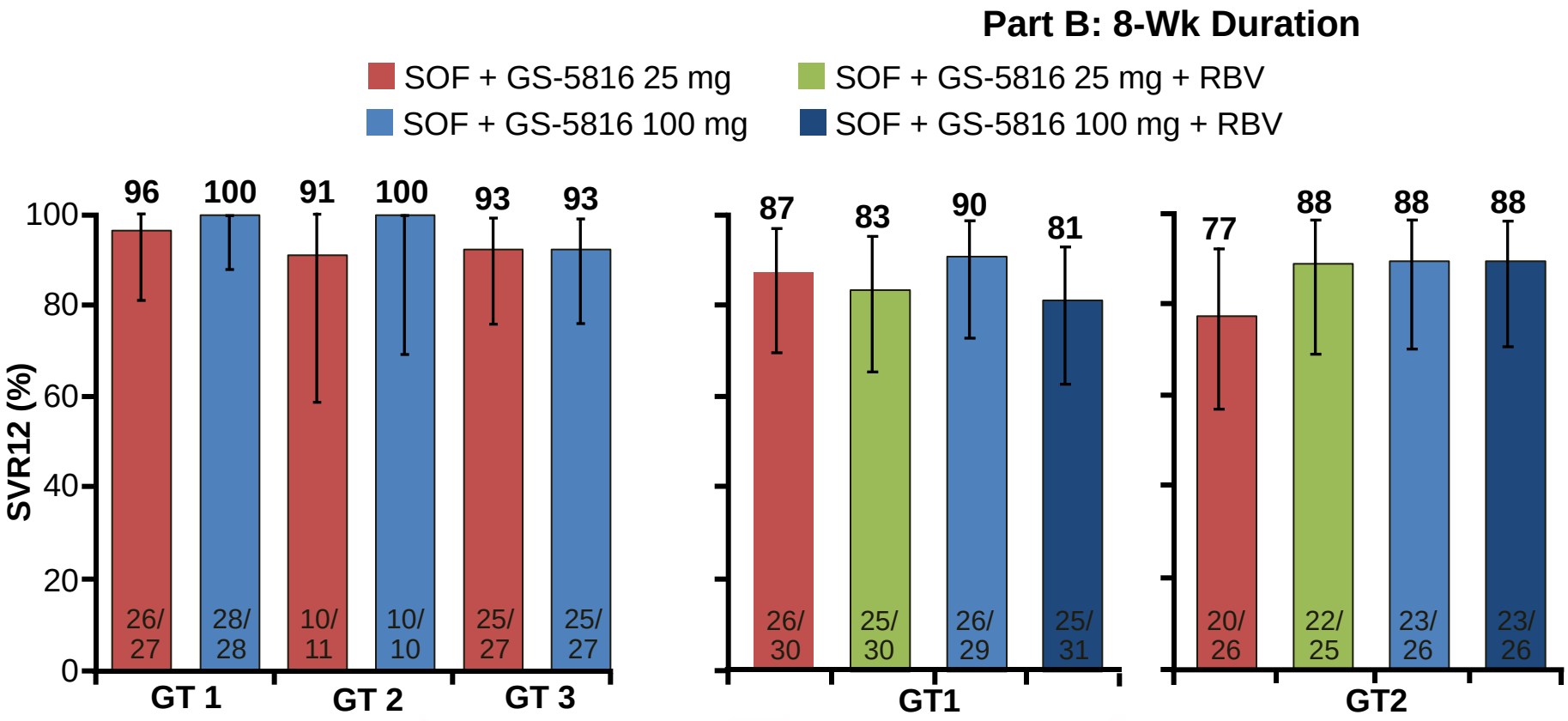
SVR Rates Reduced With 8-Wk Regimen in GT1 & 2; 12 Wks Effective in GT1, 2 and 3



Tran TT, et al. AASLD 2014. Abstract 80.

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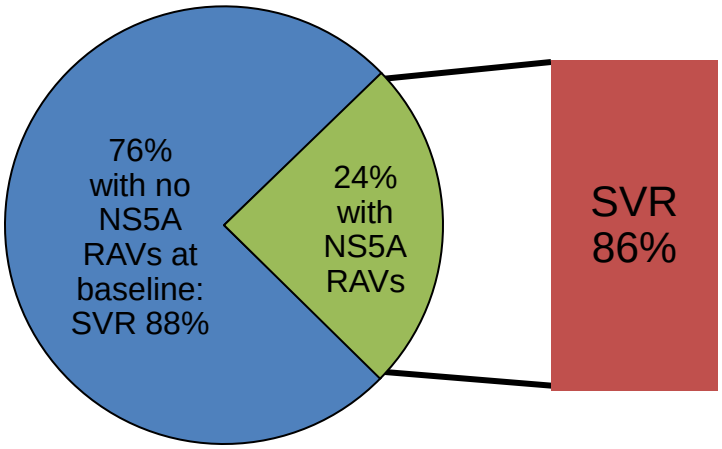
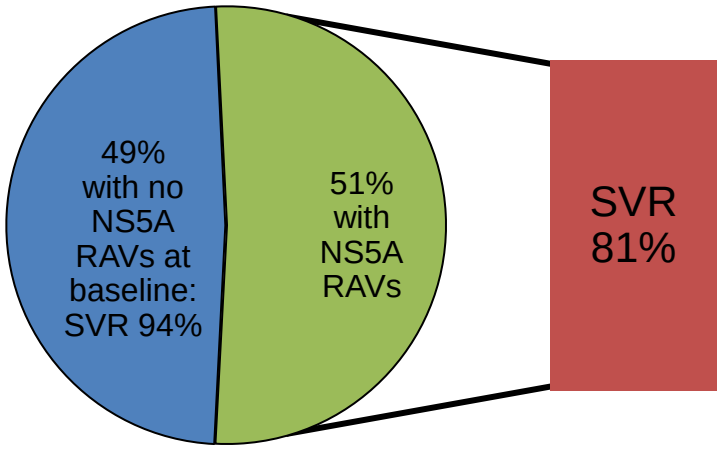
8-Wk Duration: Impact of Baseline NS5A RAVs on Efficacy

GT1 8-Wk Treatment



GT2 8-Wk Treatment



- Response rate lower in GT2 pts with baseline NS5A RAVs

Tran TT, et al. AASLD 2014. Abstract 80.

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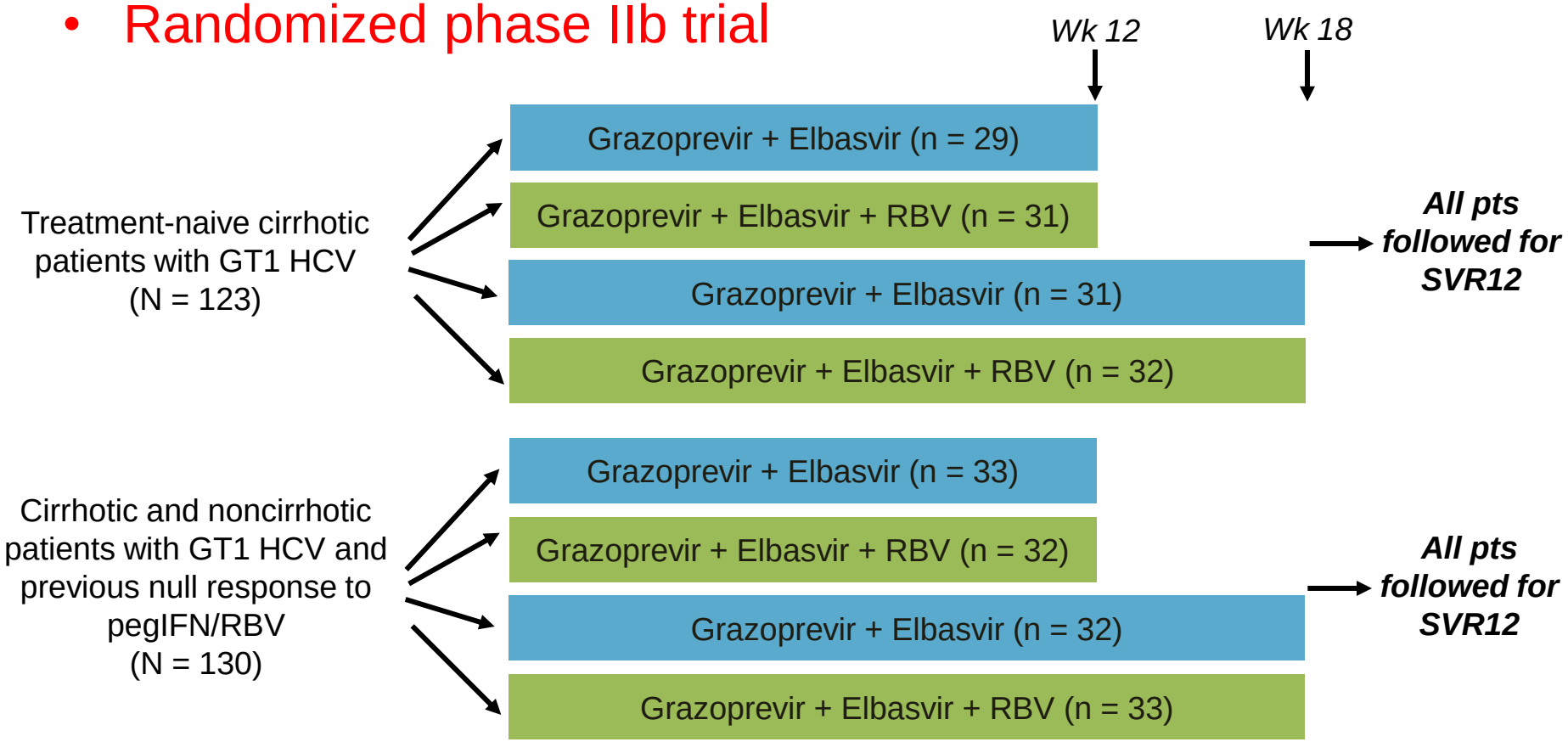
C-WORTHY: Grazoprevir + Elbasvir ± RBV x 12 or 18 Wks in GT1 HCV Pts

- Randomized phase IIb trial



Grazoprevir 100 mg once daily; elbasvir 50 mg once daily; weight-based RBV 800, 1200, or 1400 mg daily.

Lawitz E, et al. AASLD 2014. Abstract 196.

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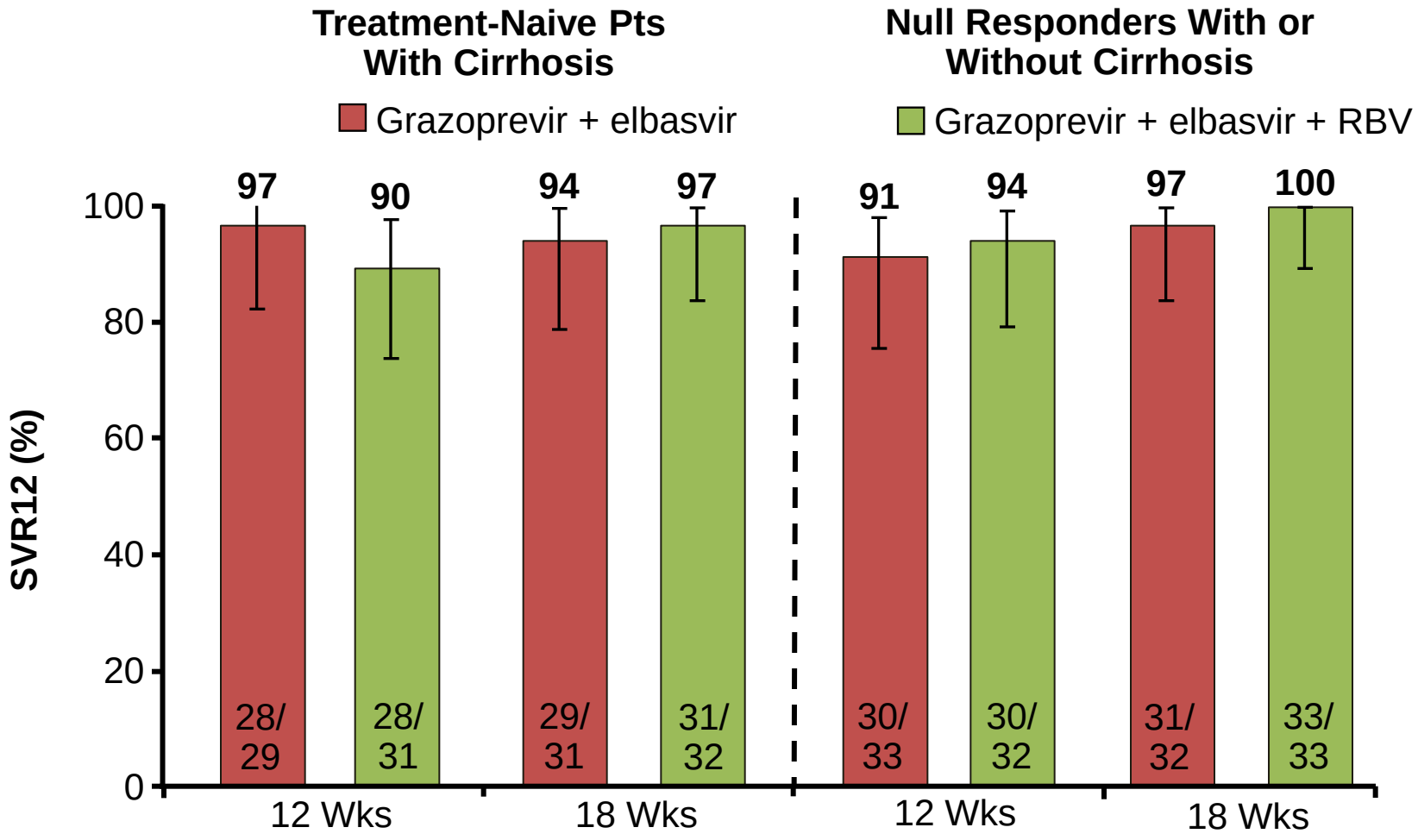
C-WORTHY: Efficacy of Grazoprevir + Elbasvir ± RBV x 12 or 18 Wks



Lawitz E, et al. AASLD 2014. Abstract 196.

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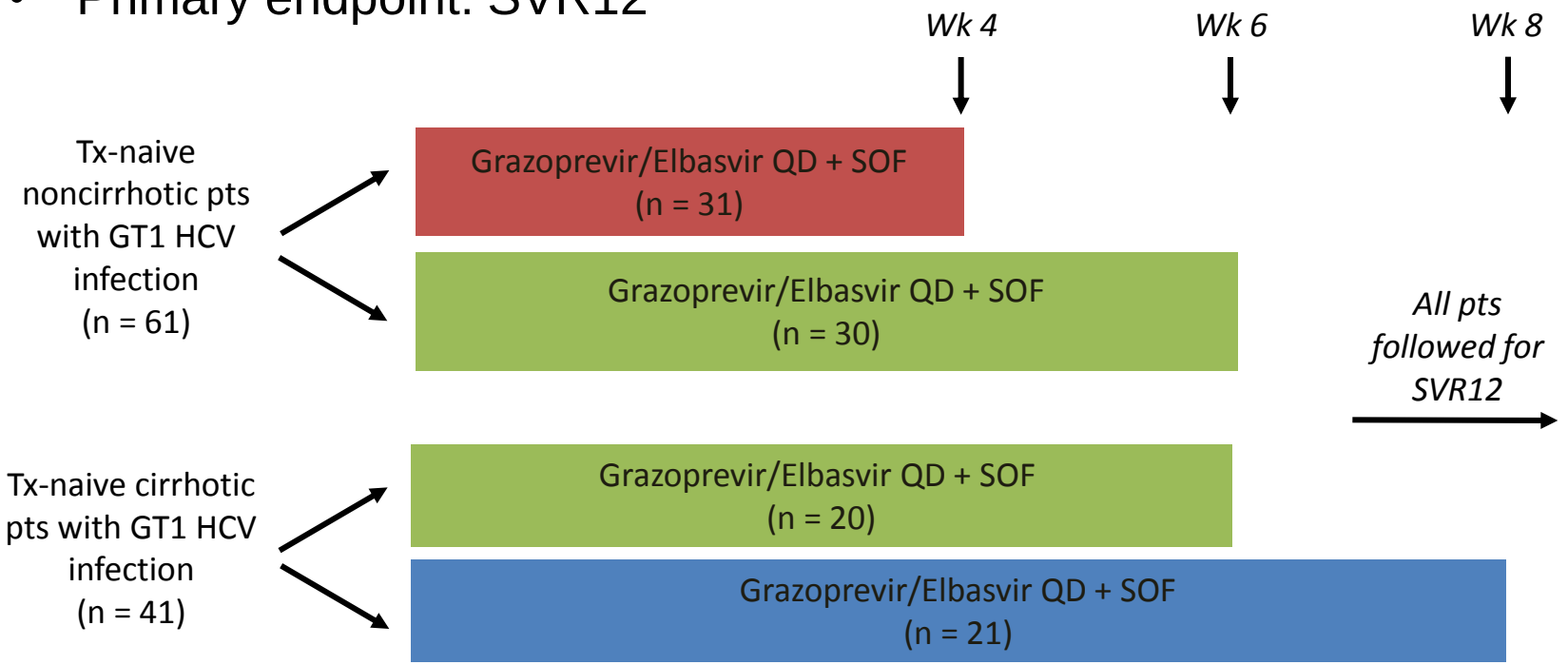
C-SWIFT: Grazoprevir/Elbasvir + SOF x 4, 6, or 8 Wks in Tx-Naive GT1 HCV

- Randomized, open-label phase II trial
- Primary endpoint: SVR12



Grazoprevir/elbasvir 100/50 mg QD FDC; sofosbuvir 400 mg QD

Lawitz E, et al. AASLD 2014. Abstract LB-33.```

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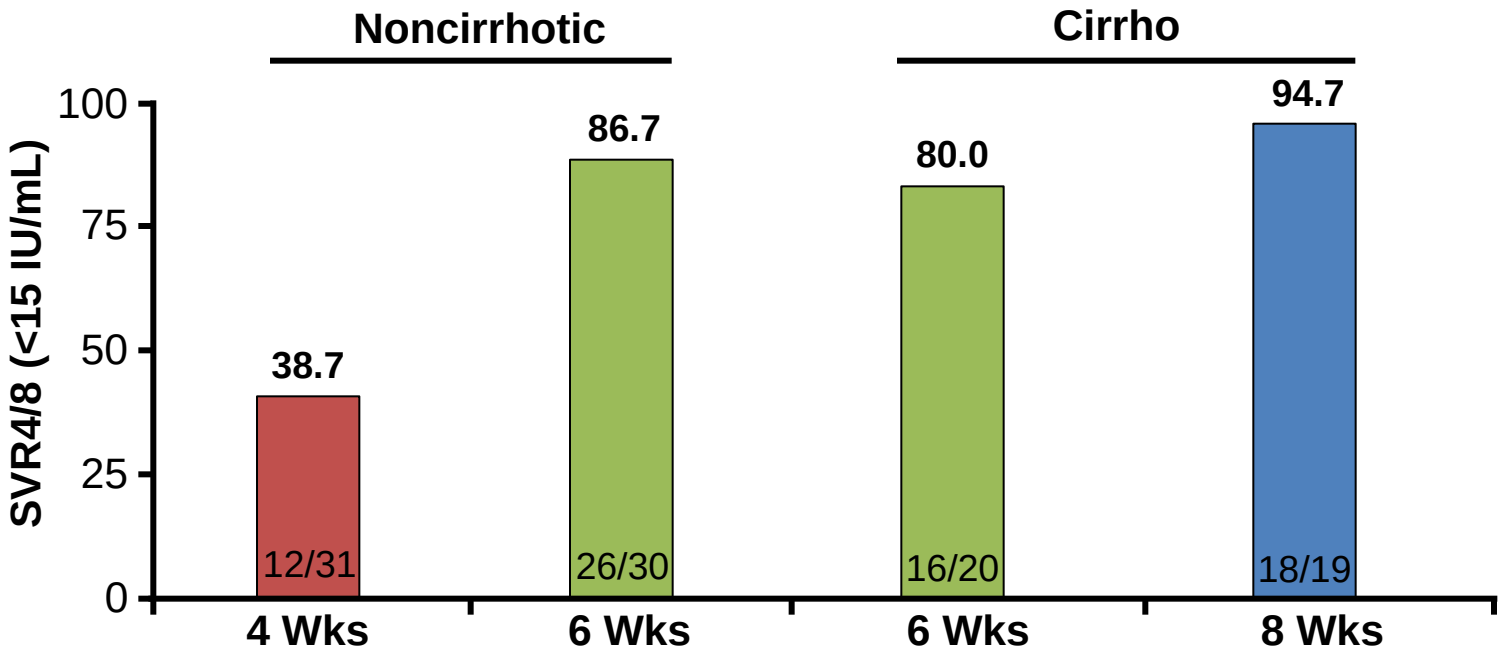
C-SWIFT Interim Results: Modified ITT SVR4/8 With Grazoprevir/Elbasvir + SOF



SVR4/8 by HCV Subtype, % (n/N)	No Cirrhosis		Cirrhosis	
	4 Wks (n = 31)	6 Wks (n = 30)	6 Wks (n = 20)	8 Wks (n = 21)
GT1a	35 (9/26)	85 (22/26)	81 (13/16)	93 (14/15)
GT1b	60 (3/5)	100 (4/4)	75 (3/4)	100 (4/4)

Lawitz E, et al. AASLD 2014. Abstract LB-33.

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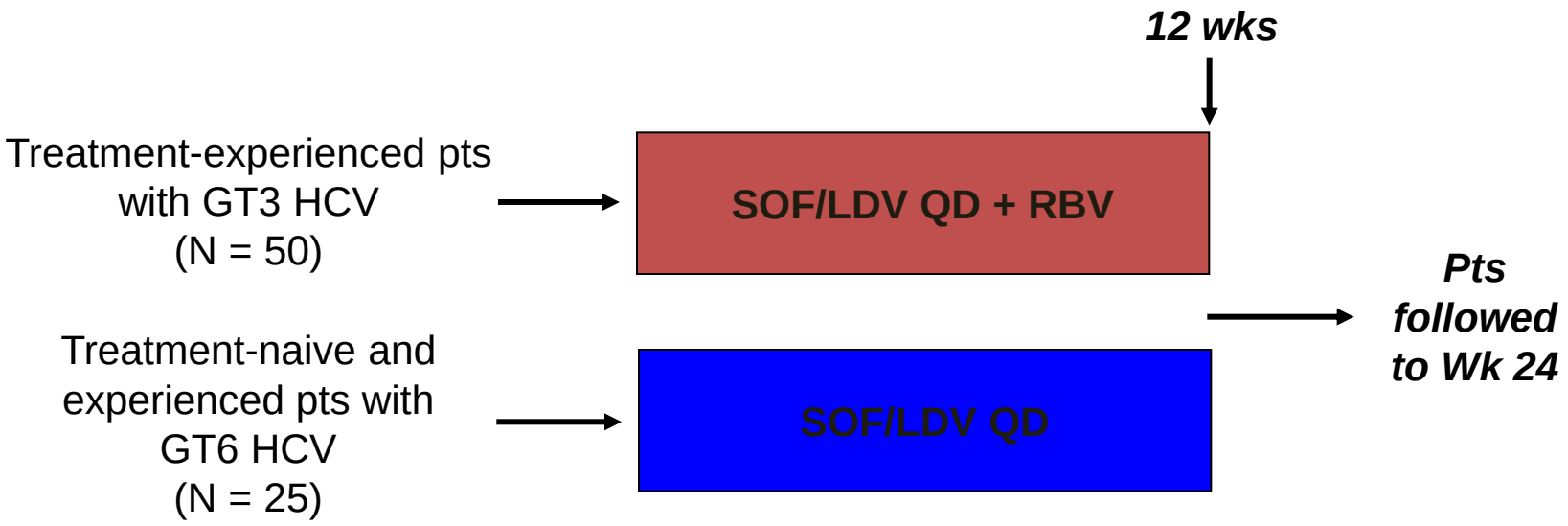
SOF/LDV ± RBV x 12 Wks in Treatment-Naive and Exp'd Pts With GT3 or 6 HCV

- Nonrandomized, open-label phase III trial
- Primary endpoint: SVR12
- Cirrhosis present in 44% GT3 pts and 8% GT6 pts



Gane EJ, et al. AASLD 2014. Abstract LB-11.

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Efficacy of SOF/LDV ± RBV x 12 Wks in Pts With GT3 or 6 HCV

SVR12, % (n/N)	GT3 Tx-Experienced Pts	GT6
Overall	82 (41/50)	96 (24/25)
By cirrhosis status	89 (25/28)	NR
▪No cirrhosis	73 (16/22)	NR
▪Cirrhosis		

- GT3 HCV remains difficult to treat, particularly in treatment-experienced cirrhotic patients

Gane EJ, et al. AASLD 2014. Abstract LB-11.

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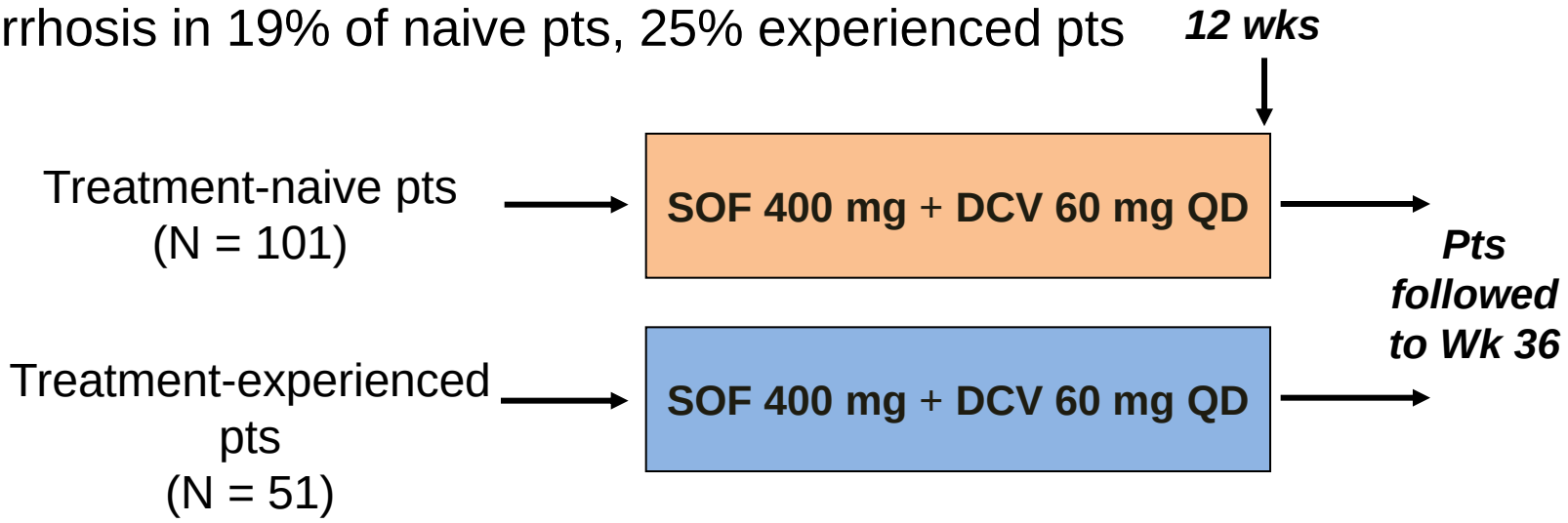
ALLY-3: SOF + DCV x 12 Wks in GT3 HCV Pts

- Primary endpoint: SVR12
- Inclusion criteria
  - 18 yrs of age or older with GT3 HCV and HCV RNA ≥ 10,000 IU/mL
  - Treatment naive or experienced (no previous NS5A inhibitor use allowed)
- Cirrhosis in 19% of naive pts, 25% experienced pts



Nelson DR, et al. AASLD 2014. Abstract LB-3.

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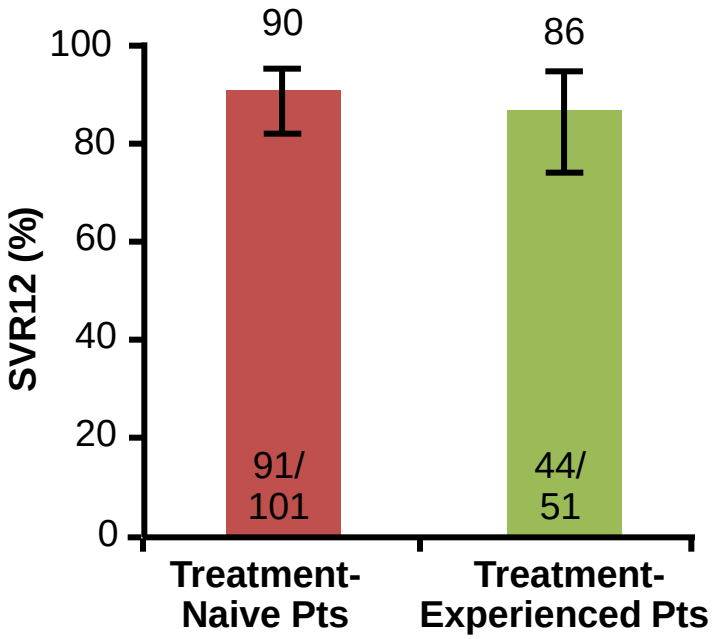
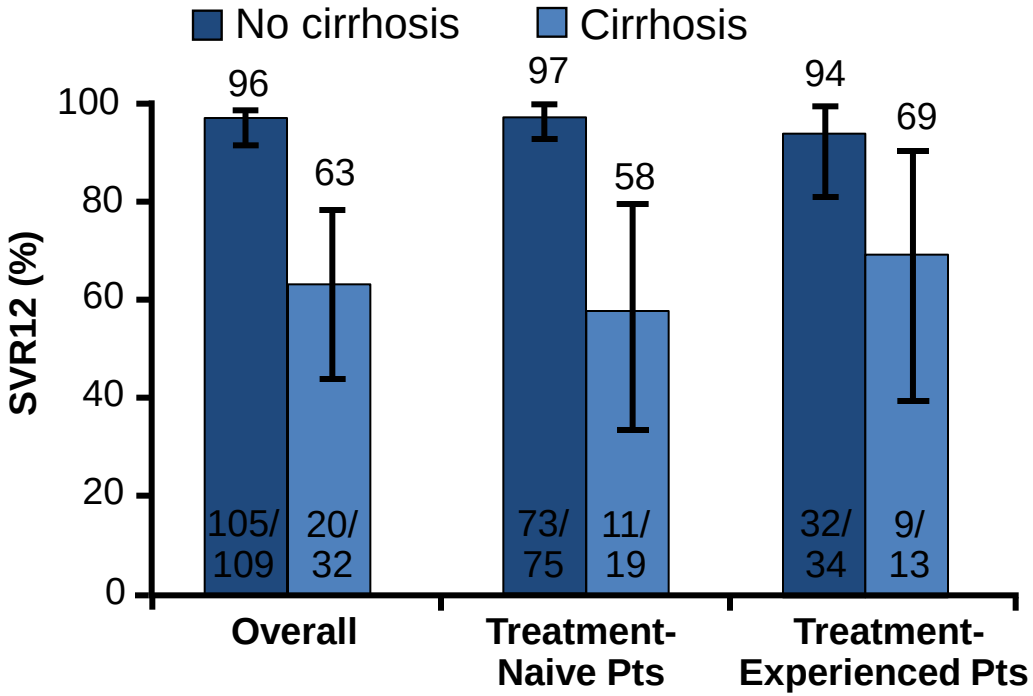
ALLY-3: SVR12 With SOF + DCV x 12 Wks in GT3 HCV Pts





- Of 16 pts with relapse, 11 had cirrhosis
- 1 of 16 relapses occurred between posttreatment Wks 4 and 12
- RAVs emerging at relapse: NS5A Y93H emerged in 9 of 16 pts

Nelson DR, et al. AASLD 2014. Abstract LB-3.

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ALLY-3: Safety and Tolerability of SOF + DCV x 12 Wks in GT3 HCV Pts

Parameter, n (%)*	All Pts (N = 152)
Death	0
Serious AEs	1 (1)†
AEs leading to discontinuation	0
Grade 3/4 AEs	3 (2)‡/0
AEs in ≥ 10% of pts (all grades)	
▪ Headache	30 (20)
▪ Fatigue	29 (19)
▪ Nausea	18 (12)
Grade 3/4 laboratory abnormalities	
▪ Hemoglobin < 9.0 g/dL	0
▪ Absolute lymphocytes < 0.5 x 10^9 /L	1 (1)
▪ Platelets < 50 x 10^9 /L	2 (1)
▪ International normalized ratio > 2 x ULN	2 (1)
▪ Lipase > 3 x ULN	3 (2)

*On-treatment events for death and AEs; treatment-emergent events for grade 3/4 laboratory abnormalities.
†1 event of gastrointestinal hemorrhage at Wk 2, considered not related to study treatment.
‡Arthralgia in 1 pt; food poisoning, nausea, and vomiting in 1 pt; and serious AE of gastrointestinal hemorrhage in 1 pt.

Nelson DR, et al. AASLD 2014. Abstract LB-3.

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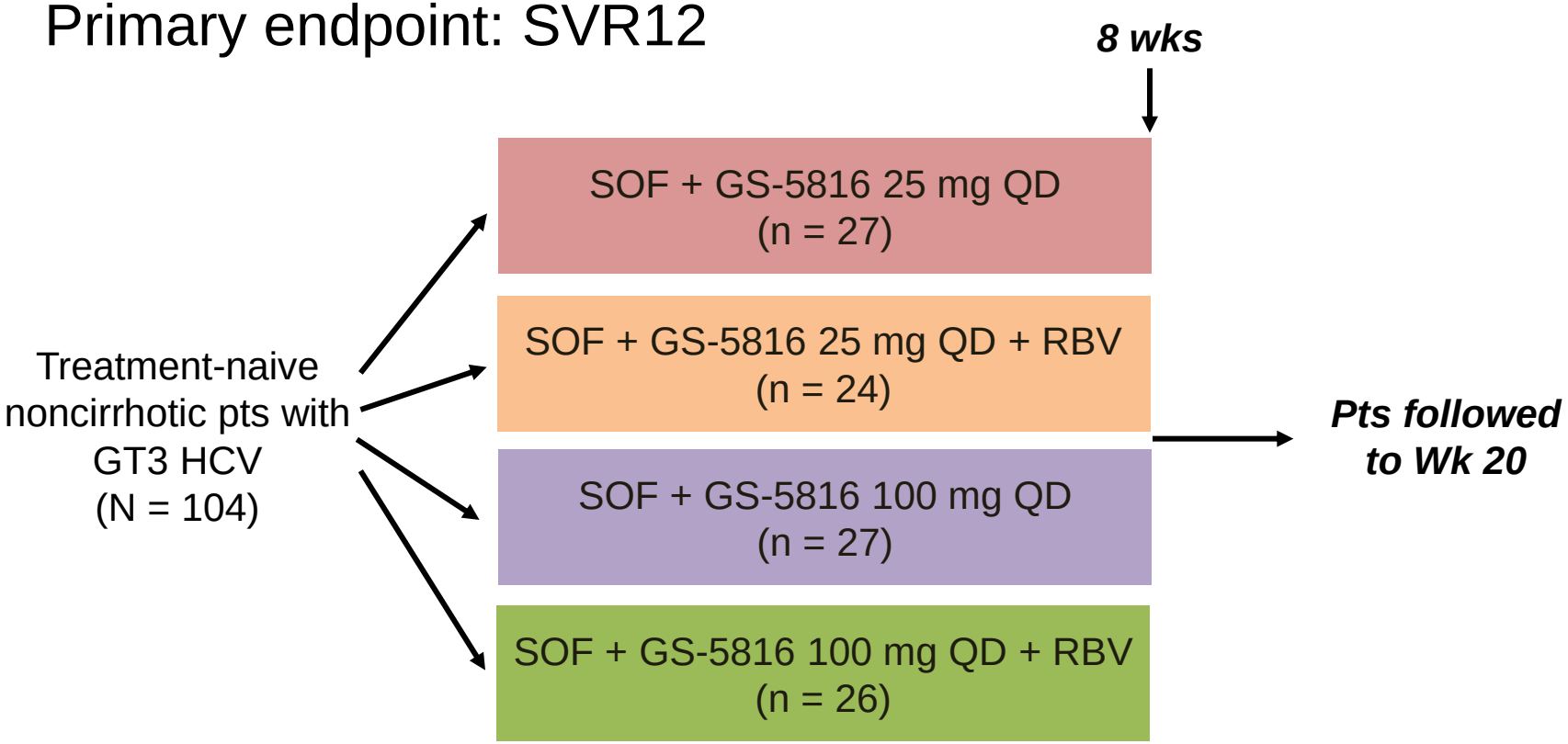
ELECTRON-2: SOF + GS-5816 ± RBV x 8 Wks in Noncirrhotic Pts With GT3 HCV

- Randomized, open-label phase II trial
- Primary endpoint: SVR12



Gane EJ, et al. AASLD 2014. Abstract 79.

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ELECTRON-2: SVR12 With SOF + GS-5816 ± RBV x 8 Wks in Noncirrhotic GT3 Pts

SVR12, % (n/N)	GT3 Noncirrhotic Patients			
	SOF + GS-5816 25 mg (n = 27)	SOF + GS-5816 25 mg + RBV (n = 24)	SOF + GS-5816 100 mg (n = 27)	SOF + GS-5816 100 mg + RBV (n = 26)
Overall	100	88	96	100

- Baseline NS5A RAVs had no effect on efficacy

Gane EJ, et al. AASLD 2014 Abstract 79

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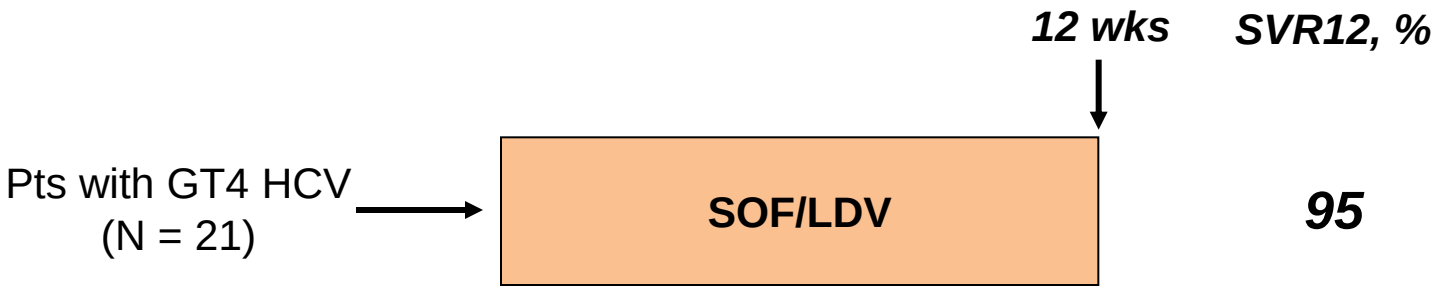
SYNERGY Trial: SOF/LDV x 12 Wks in Patients With GT4 HCV

- Single-center, open-label phase IIa trial
- Primary endpoint: SVR12
- 38% of pts were treatment experienced; all were naive to DAAs
- 33% had cirrhosis
- No deaths, serious AEs, or grade 4 laboratory events; 1 d/c



Kapoor R, et al. AASLD 2014. Abstract 240.

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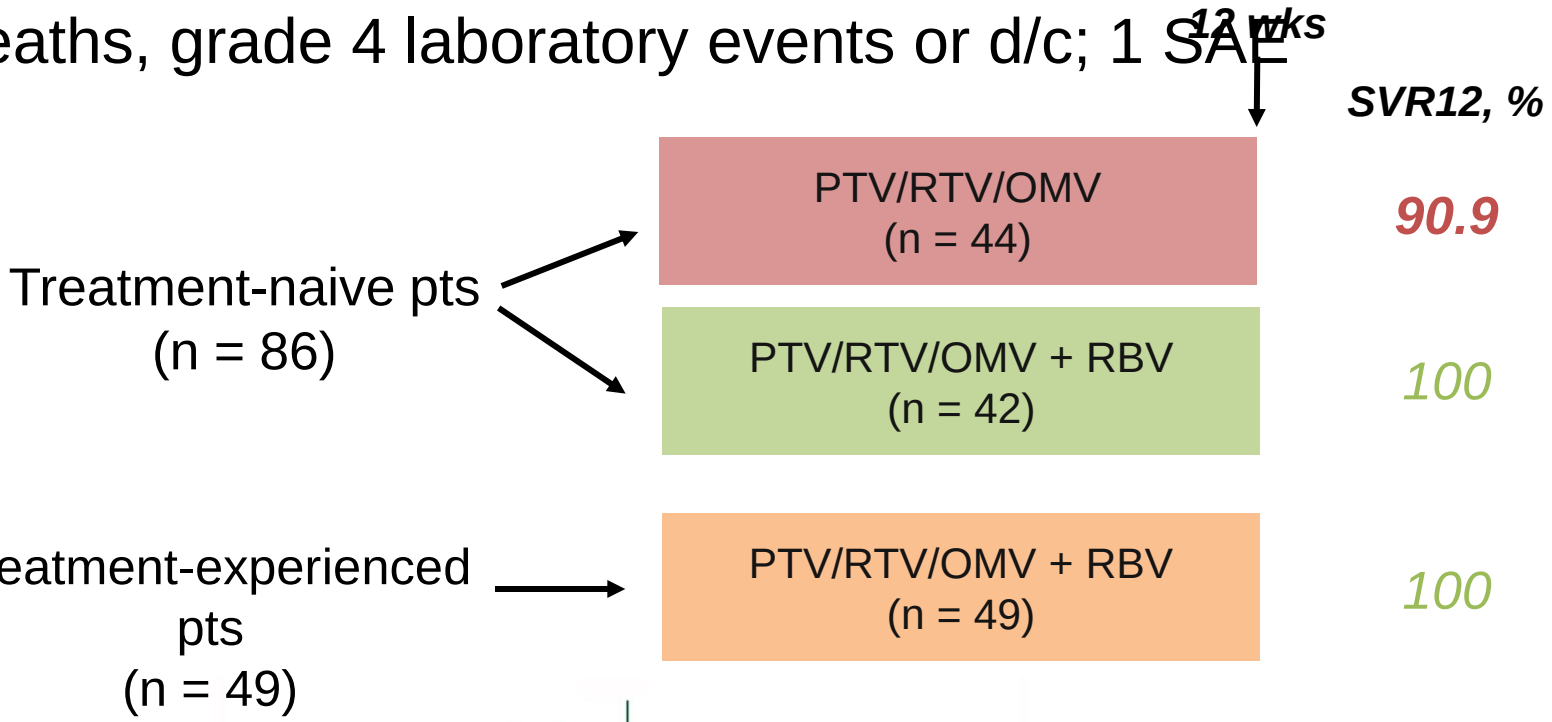
PEARL-I: PTV/RTV/OMV ± RBV x 12 Wks in Patients With GT4 HCV

- Randomized, open-label phase IIb trial
- Primary endpoint: SVR12
- Cirrhotic patients excluded
- No deaths, grade 4 laboratory events or d/c; 1 SAE



Pol S, et al. AASLD 2014. Abstract 1928.

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Indications and Use of Ombitasvir/ Paritaprevir/Ritonavir and Dasabuvir

- Approved for genotype 1 HCV infection only, with or without compensated cirrhosis
- Can be used in liver transplant recipients with normal hepatic function, Metavir ≤ 2
- Regimen components
  - Ombitasvir: NS5A inhibitor
  - Paritaprevir: NS3/4 protease inhibitor with ritonavir boosting via CYP3A inhibition
  - Dasabuvir: nonnucleoside NS5B polymerase inhibitor
- Taken as 2 FDC ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg) tablets QD and 1 dasabuvir tablet (250 mg) BID
  - Taken with a meal; no specific limitations on fat or calorie content
  - Weight-based ribavirin dosing: 1000 mg if ≤ 75 kg, 1200 mg if > 75 kg
    - Dosage divided and taken BID with food
  - No dose adjustment for hepatic or renal impairment or for HCV/HIV coinfection

Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

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Recommended Regimen Design According to Patient Population

- Duration and inclusion of ribavirin vary according to patient population
  - GT1 subtype, presence of cirrhosis
  - If subtype is unknown or is mixed, use as described for GT1a
- HIV coinfection: use regimen and duration as described for HCV monoinfection

Population	Regimen	Duration
GT1a, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV + RBV	12 wks
GT1a, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV	24 wks*
GT1b, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV	12 wks
GT1b, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV	12 wks
GT1, post-OLT (Metavir ≤ 2)	OMV/PTV/RTV + DSV + RBV	24 wks

*12-wk course may be considered for some patients based on previous treatment history.

Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

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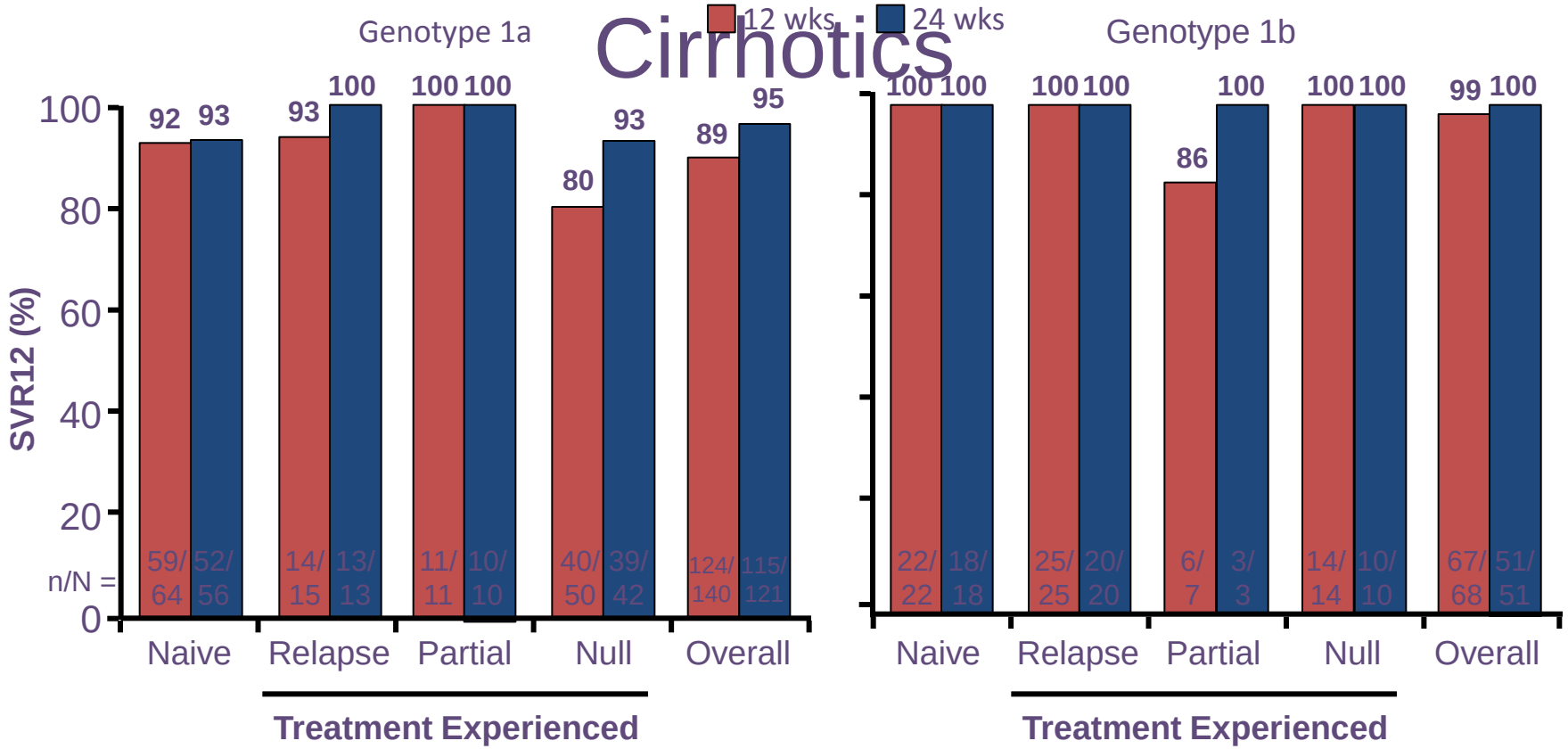
Contraindications and Selected Precautions

- Not recommended for decompensated cirrhosis
  - CTP-B: not recommended
  - CTP-C: contraindicated
- Not studied in dialysis patients; no dosage adjustment needed in patients with creatinine clearance ≥ 15 mL/min
- Contraindicated with drugs dependent on CYP3A for clearance, strong CYP3A and CYP2C8 inducers, strong CYP2C8 inhibitors
- Ribavirin contraindications and warnings/precautions apply
- Avoid if known hypersensitivity to ritonavir
- HCV/HIV coinfection: risk of HIV PI resistance
  - Coinfected patients should be receiving suppressive ART

Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

TURQUOISE II: 12 vs 24 Wks of OMV/PTV/RTV + DSV + RBV in Cirrhotics



Poordad F, et al. EASL 2014. Abstract O163. Poordad F, et al. N Engl J Med. 2014;370:1973-1982. Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

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Warnings and Precautions: ALT Elevations

- ALT elevations of > 5 x ULN seen in ~ 1% of pts in clinical trials
  - More common in women receiving ethinyl estradiol–containing treatment
  - Typically asymptomatic, in first 4 wks of therapy, declined in 2-8 wks with continued dosing of OMV/PTV/RTV + DSV
- Discontinue ethinyl estradiol prior to use of OMV/PTV/RTV + DSV
  - May resume 2 wks after stopping OMV/PTV/RTV + DSV
- Coadminister with caution in pts receiving other estrogens
- Monitor hepatic labs at baseline, in first 4 wks, and after as needed
  - Repeat and monitor if ALT elevated above baseline levels
  - Consider discontinuation if ALT persistently > 10 x ULN; discontinue if ALT elevation accompanied by liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR

Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

All-Oral Regimens for Other Populations

Refer to www.hcvguidelines.org for further information on how to use these therapies

1. Sofosbuvir [package insert]. 2. Ombitasvir/paritaprevir/ritonavir plus dasabuvir [package insert].
3. AASLD/IDSA HCV Guidelines. Accessed January 5, 2015

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Acknowledgments

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Program Director

Paul Y. Kwo, MD
Professor of Medicine
Medical Director of Transplantation
Division of Medicine/ Gastroenterology/Hepatology
Indiana University School of Medicine
Indianapolis, Indiana

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Thank You

Dushyantha Jayaweera MD, MRCOG(UK) FACP

Associate Vice Provost for Human Subject Research

Professor of Clinical Medicine

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