
12TH ANNUAL
NCSCG
POST-DDW
SYMPOSIUM

Viral Hepatitis

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Disclosures

- Consultant/Advisory Board – Gilead, BMS, AbbVie
- Research – Gilead

- Off-label use of investigational agents will be discussed
- Off label-use of currently FDA-approved agents will be discussed
- Data from EASL and DDW 2015

Outline

- HCV Treatment
  - Cirrhosis
  - GT 1 vs. GT 3 vs. other GT
  - Decompensated cirrhosis
  - Post-liver transplant
  - Renal failure
  - Future regimens
  - Resistance
- HBV Treatment

Approved DAAs and DAAs in Clinical Development

Table 1. Approved DAAs and DAAs in clinical development at the beginning of 2015.

Agent class	Generation	Compound	Phase of clinical development
NS3-4A protease inhibitors	First-wave, first-generation	Telaprevir Boceprevir	Approved
	Second-wave, first-generation	Simeprevir Paritaprevir/r	Approved
		Asunaprevir Vaniprevir Vedroprevir Sovaprevir	In clinical development
	Second-generation	Grazoprevir ACH-2684 GS-9857	In clinical development
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir	Approved
		MK-3682 ACH-3422 AL-335	In clinical development
Non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase	Palm domain I inhibitors	Dasabuvir	Approved
	Thumb domain I inhibitors	Beclabuvir	In clinical development
	Thumb domain II inhibitors	GS-9669	In clinical development
NS5A inhibitors	First-generation	Daclatasvir Ledipasvir Ombitasvir	Approved
	Second-generation	Elbasvir GS-5816 ACH-3102	In clinical development

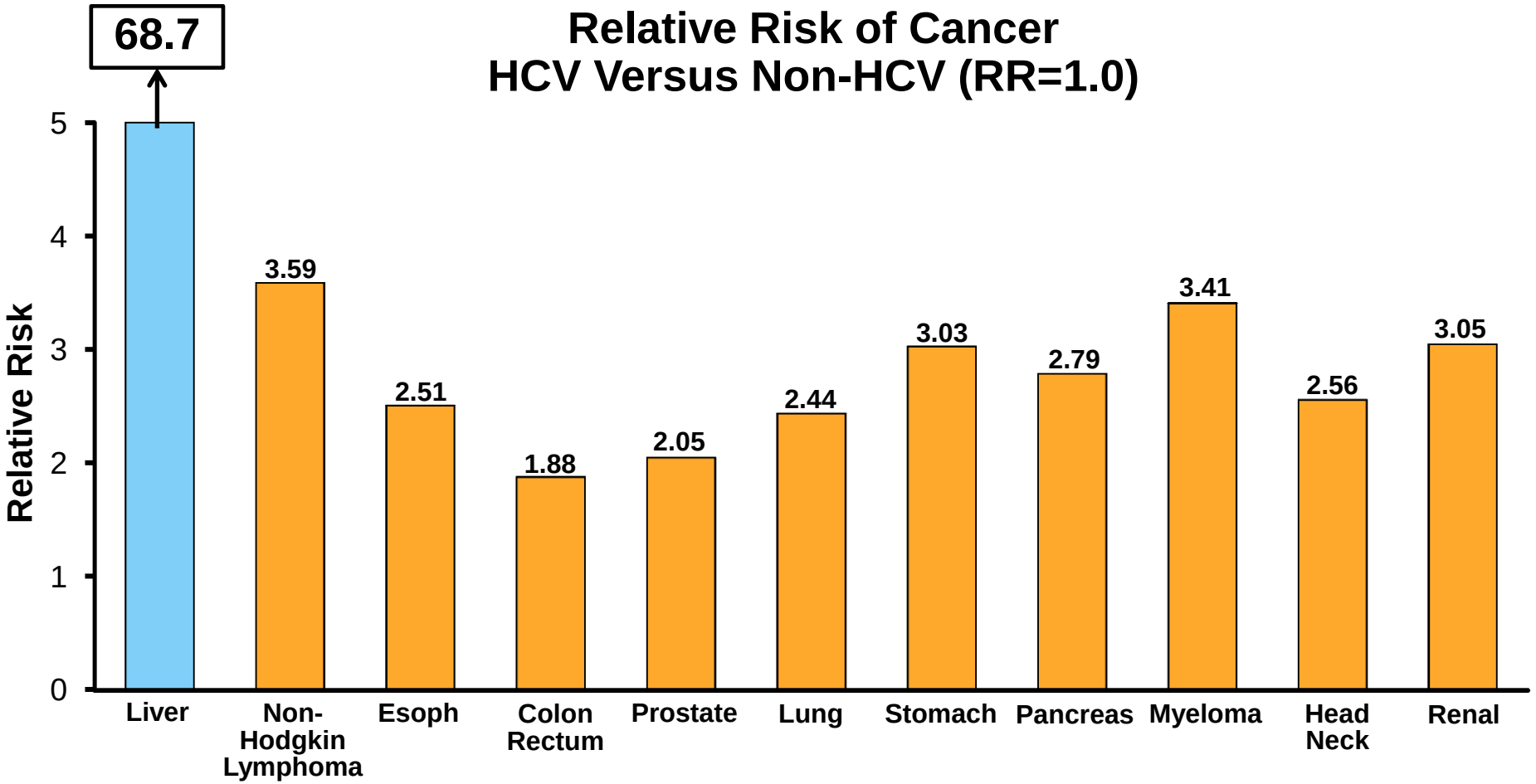
/r, ritonavir-boosted.

Adapted from Pawlotsky JM et al. J of Hepatology 2015; 62: S87-S99.

HCV

- Are there reasons other than stage of liver disease to treat HCV?

Increased Cancer Rates in Patients with Chronic HCV: An Analysis of the Cancer Registry in a Large US HMO (A. Nyberg et al. Abstract O058)



P<0.000 versus non-HCV for all cancers.
HCV with cancer (n=1831); HCV without cancer (n=33,881); no HCV (n=5,297,191).
HCV diagnosis: ICD-9 code or positive HCV RNA test. Patients with HIV were excluded.

Nyberg AH, et al. *J Hepatol.* 2015;62(suppl 2):S220. Abstract O058.

HCV - SVR

- Is a sustained virologic response really that sustained?

HCV Reinfection in Phase 3 Studies of Sofosbuvir-Containing Regimens (Svarovskaia E et al. Abstract O063)

- 99.6% concordance of SVR12 (n=3004) and SVR24 (n=2992) in sofosbuvir clinical studies
- 12 patients did not achieve SVR24
  - Full-length NS5B successfully deep sequenced (n=10)
  - Only short NS5B fragment sequenced due to low HCV viral load (n=2)
- Of the 12 discordant cases
  - Late relapse (n=5): minimal genetic drift between baseline and posttreatment week 24 samples
  - Reinfection (n=7)

Svarovskaia E, et al. *J Hepatol.* 2015;62(suppl 2):S222-S223. Abstract O063.

HCV – “Sim+Sof”

- Now that Simeprevir + Sofosbuvir is FDA approved, can I try to shorten the regimen?
- For non-cirrhotic patients?
- How about for cirrhotic patients?

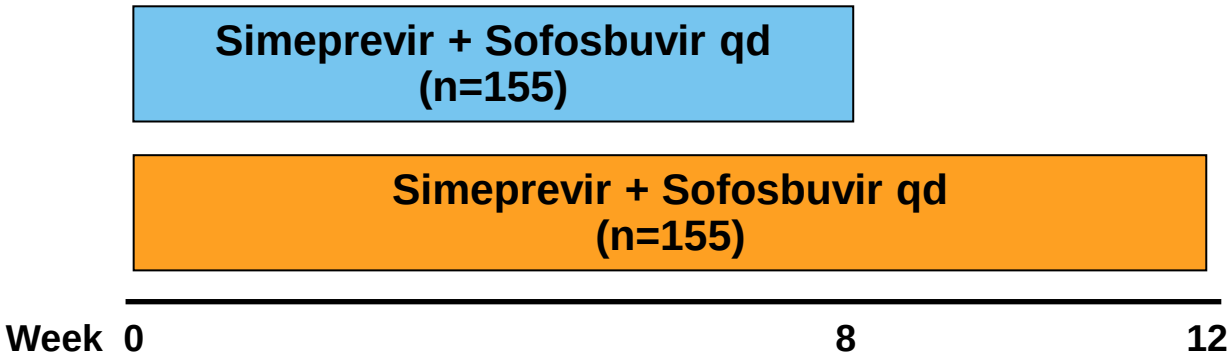
Simeprevir plus sofosbuvir indicated for GT1 for

- 12 weeks in non-cirrhotic patients (naïve or experienced)
- 24 weeks in cirrhotic patients (naïve or experienced)

A phase 3, randomized, open-label study to evaluate the efficacy and safety of 8 and 12 weeks of simeprevir plus sofosbuvir in treatment-naïve and -experienced patients with chronic HCV genotype 1 infection **without cirrhosis**: OPTIMIST-1. (Kwo et al. Abstract LP14)

Phase 3

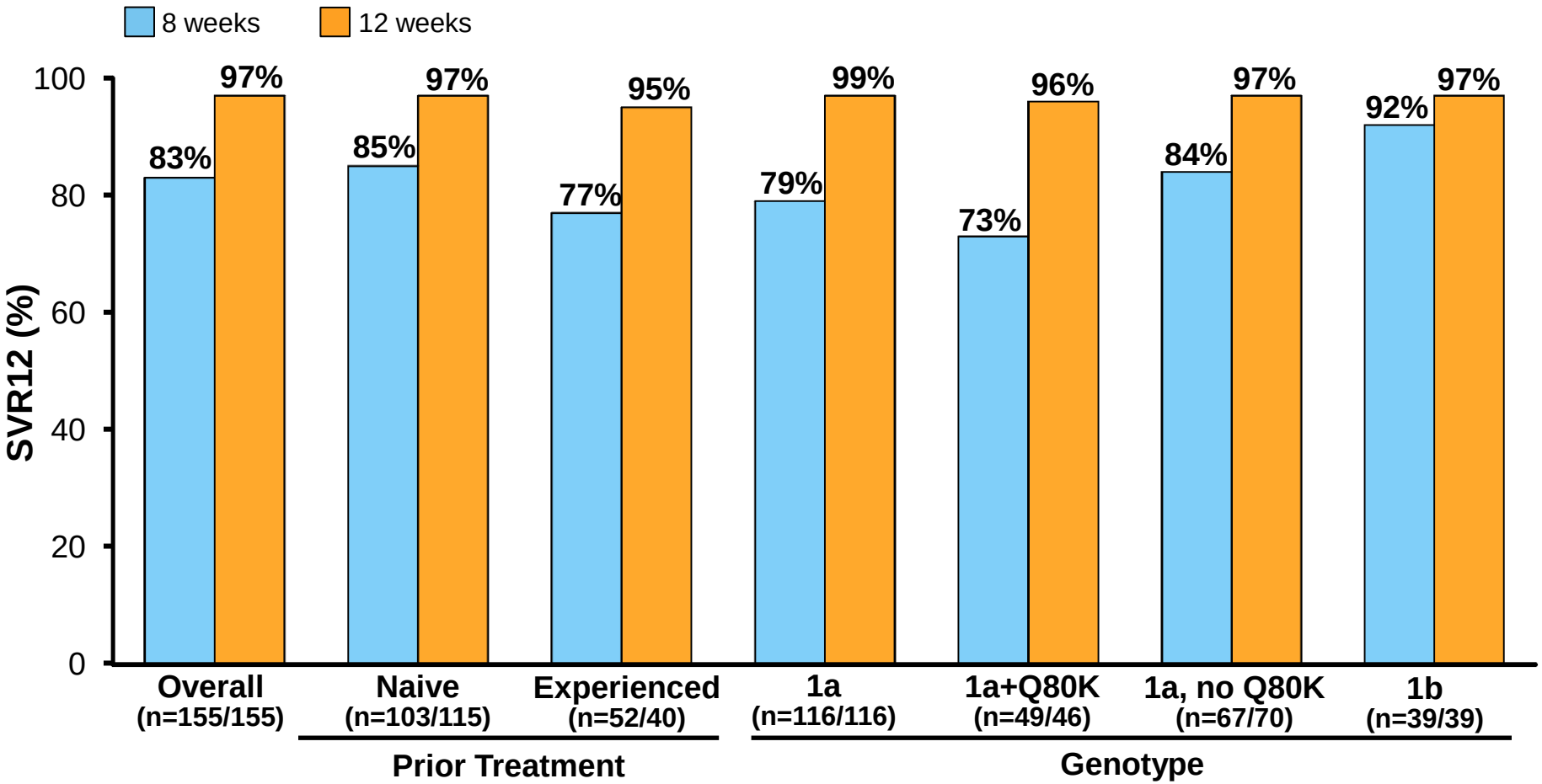
Open-label
Treatment-naïve or pegIFN-experienced
Genotype 1
No cirrhosis
Primary endpoint: SVR12



Simeprevir 150 mg daily + Sofosbuvir 400 mg daily
No ribavirin
Baseline demographics:
- Male: 53%-56%
- Mean age: 56 years
- Black: 15%-20%
- Genotype 1a: 75%
- HCV RNA (log_{10} IU/mL): 6.8
- Treatment-naïve: 66%-74%

Kwo P, et al. *J Hepatol.* 2015;62(suppl 2):S270. Abstract LP14.

A phase 3, randomized, open-label study to evaluate the efficacy and safety of 8 and 12 weeks of simeprevir plus sofosbuvir in treatment-naïve and -experienced patients with chronic HCV genotype 1 infection without cirrhosis: OPTIMIST-1. (Kwo et al. Abstract LP14)



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- Patients not achieving SVR12 (10%; 31/309)
  - No breakthroughs
  - Relapse
    - 8-week arm (17%, 27/155): lower relapse rate with baseline HCV RNA <4 million IU/mL
    - 12-week arm (3%, 4/154)
- Safety
  - Well tolerated, most adverse events were grade 1 or 2
    - Most common: nausea, headache, fatigue
  - No discontinuations due to adverse events
  - No grade 3/4 changes in bilirubin or hemoglobin values

Kwo P, et al. *J Hepatol.* 2015;62(suppl 2):S270. Abstract LP14.

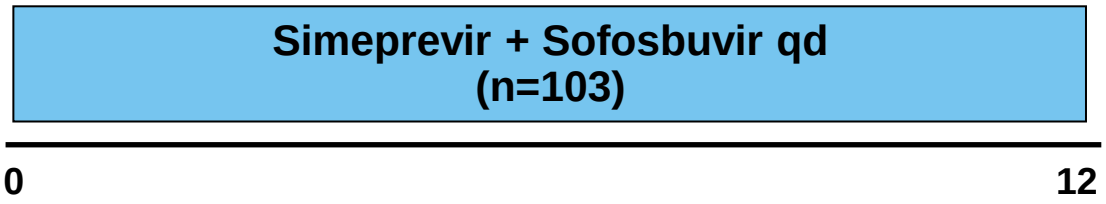
HCV – “Sim+Sof”

- Now that Simeprevir + Sofosbuvir is FDA approved, what can I expect if I try to shorten the regimen?
- For non-cirrhotic patients?
- How about for cirrhotic patients?

Simeprevir plus sofosuvir indicated for GT1 for

- 12 weeks in non-cirrhotic patients (naïve or experienced)
- 24 weeks in cirrhotic patients (naïve or experienced)

A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir plus sofosbuvir in treatment-naïve or -experienced patients with chronic HCV genotype 1 infection and **cirrhosis**: OPTIMIST-2. (Lawitz et al. Abstract LP04)



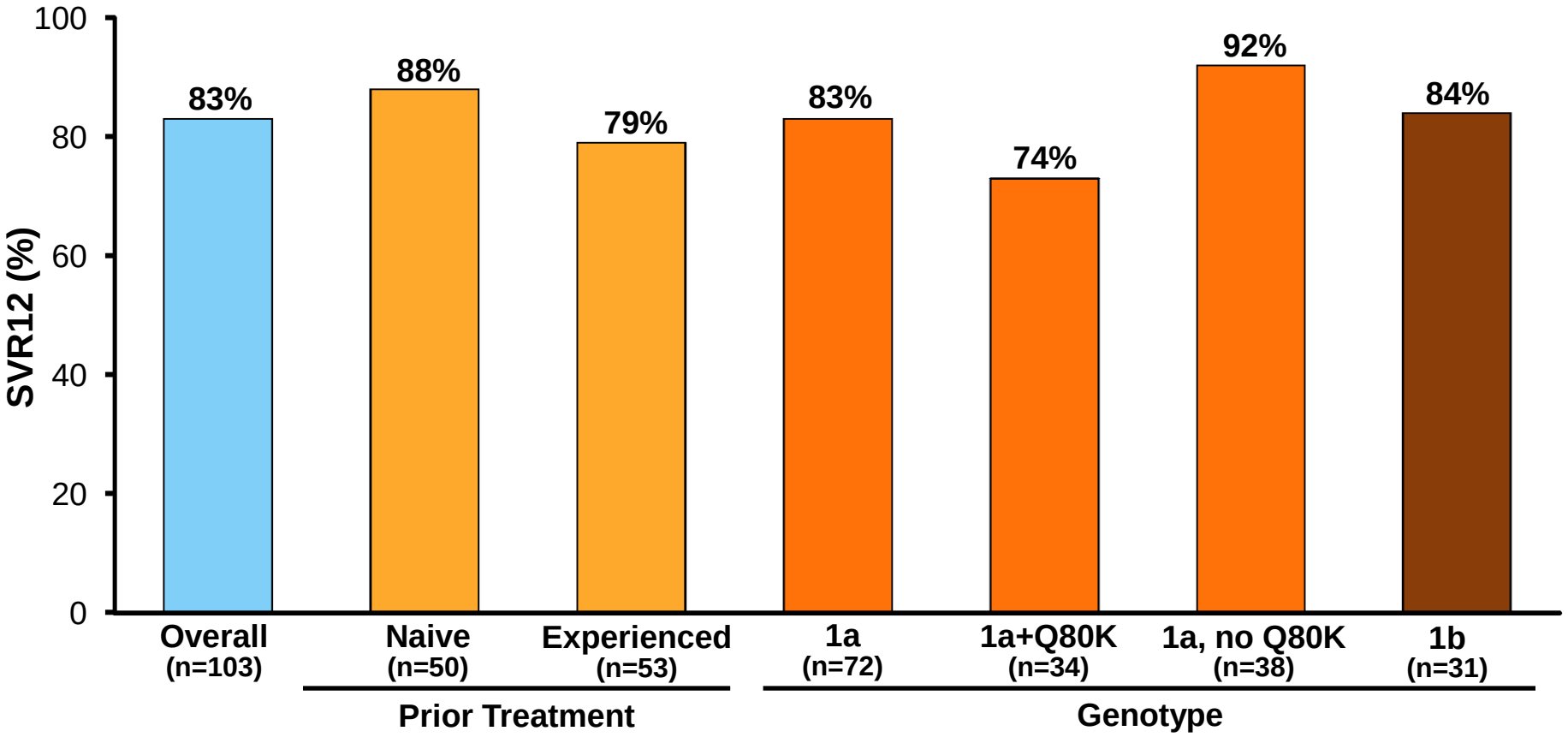
Phase 3

Open-label
Treatment-naïve or experienced
Genotype 1
Platelets >50K/mm^3
Albumin >3 g/dL
Cirrhotics only (FibroScan, FibroTest, or biopsy)
Primary endpoint: SVR12

Simeprevir 150 mg daily + sofosbuvir 400 mg daily
No ribavirin
Baseline demographics:
- Male: 81%
- Mean age: 58 years
- Genotype 1a: 70%
- HCV RNA (log_{10} IU/mL): 6.8
- Treatment-naïve: 49%
- Albumin <4 g/dL: 51%
- Platelets <90K/mm^3: 18%

Lawitz E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP04.

A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir plus sofosbuvir in treatment-naïve or -experienced patients with chronic HCV genotype 1 infection and cirrhosis: OPTIMIST-2. (Lawitz et al. Abstract LP04)



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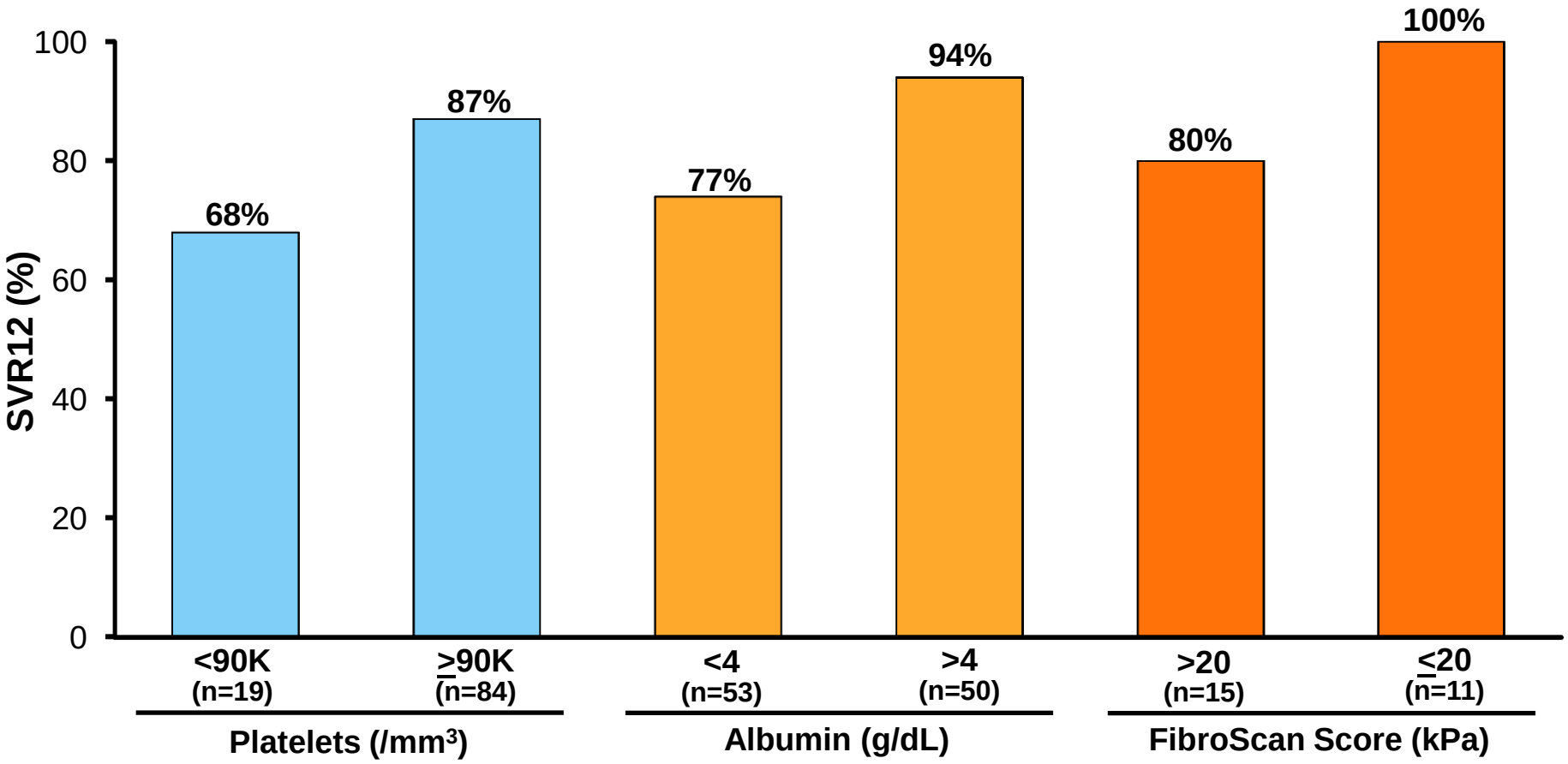

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- Patients not achieving SVR12 (17%; 17/103)
  - Breakthrough (n=3)
  - Relapse (n=13)
    - More common in those with baseline platelets <90K/mm^3, albumin <4 g/dL, FibroScan >20 kPa
  - Majority had emerging NS3 mutations
- Safety
  - Well tolerated, most adverse events were grade 1 or 2
    - Most common: headache, fatigue, nausea
  - Discontinuations due to adverse events: 3%

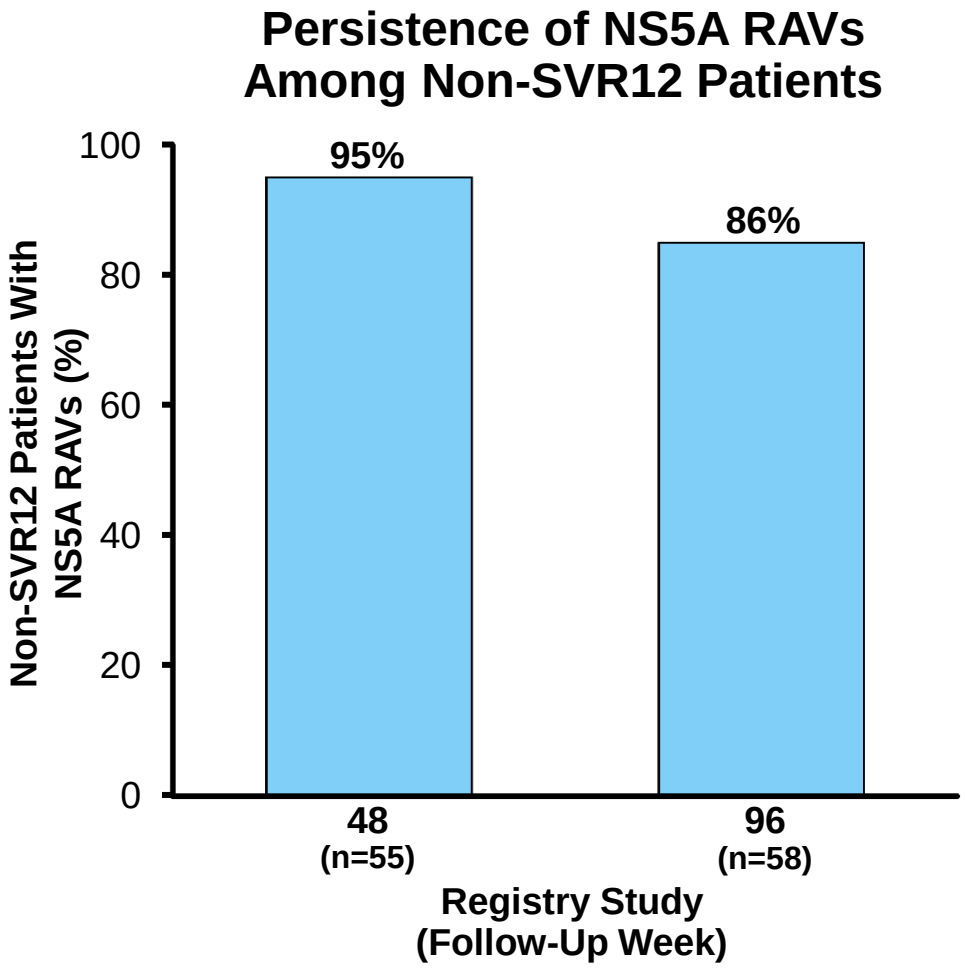
Lawitz E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP04.

HCV Resistance

- What is a RAV?
- Does resistance really matter for HCV?
- How long do these mutations stick around?

Long-term persistence of HCV NS5A variants after treatment with NS5A inhibitor ledipasvir. (H. Dvory-Sobol et al. Abstract O059)

- RAVs in non-SVR12 patients after receiving ledipasvir (without SOF) followed in a 3-year registry study
  - Performed via deep sequencing
  - Baseline NS5A RAVs (16%)
  - NS5A RAVs at treatment failure (99%)

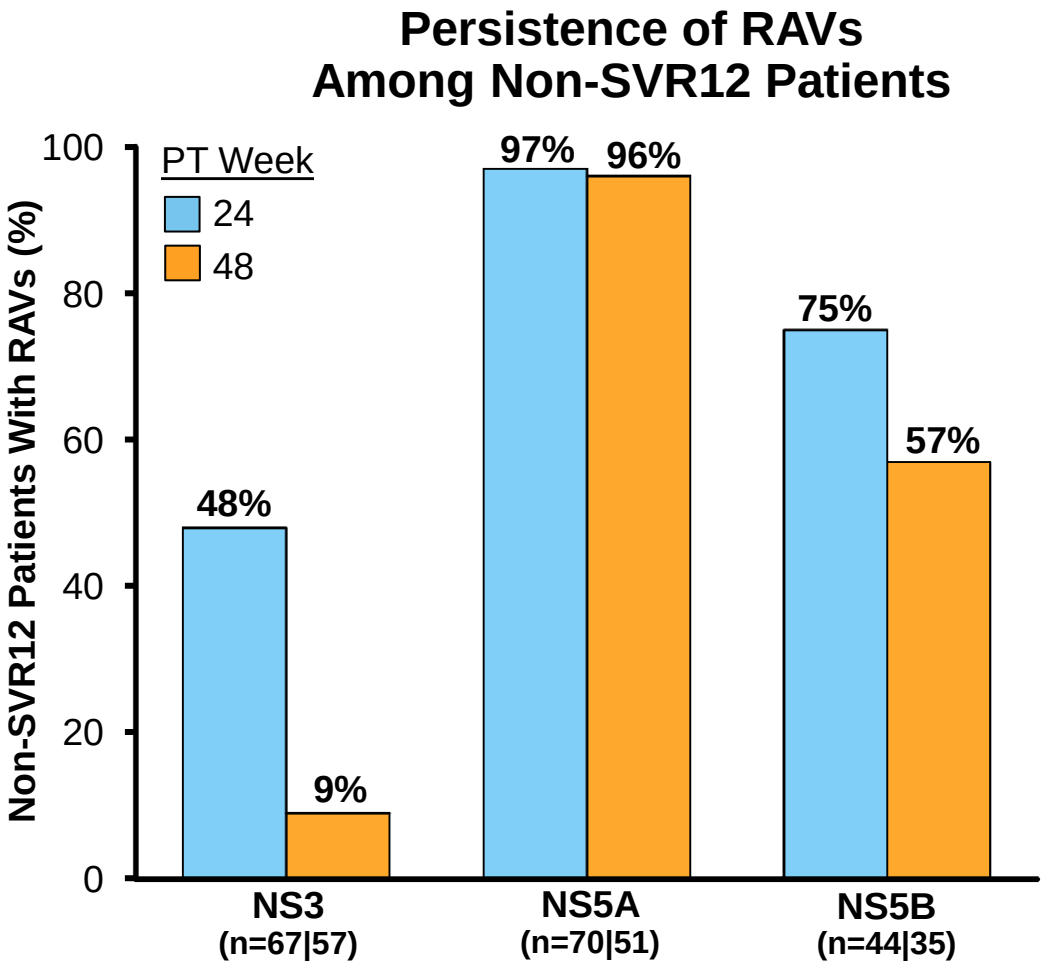


Dvory-Sobol H, Wyles D, Ouyang W, et al. *J Hepatol.* 2015;62(suppl 2):S221. Abstract O059.

RAV, resistance-associated variant

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B with paritaprevir/r-, ombitasvir- and dasabuvir-based regimens. (Krishnan et al. Abstract O057)

- Non-SVR12 patients in Phase 2 and 3 clinical trials (2.9% of pooled population)
  - Data only available for genotype 1a
  - Population sequencing
- Rate of decline of RAVs not affected by treatment duration nor treatment regimen



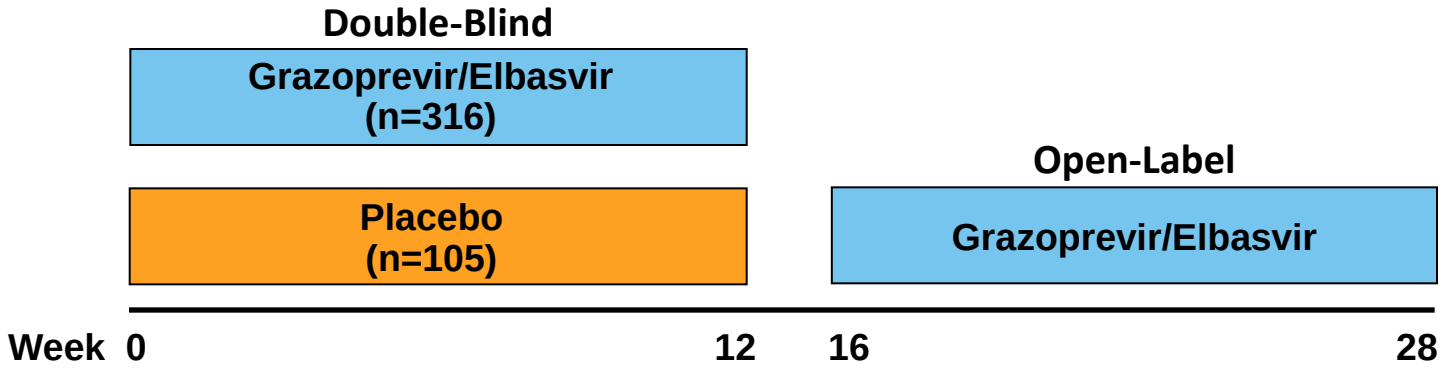
PT, post-treatment

Krishnan P, et al. *J Hepatol.* 2015;62(suppl 2):S220. Abstract O057.

HCV - Future

- What's on the horizon?
- Are these new medications going to allow for shorter therapy?
- What about for patients who have already failed other DAA regimens?

The phase 3 C-EDGE treatment-**naïve** study of 12-week regimen of grazoprevir/elbasvir in patients with chronic HCV genotype 1, 4, or 6 infection. (Zeuzem et al. Abstract G07)



Phase 3

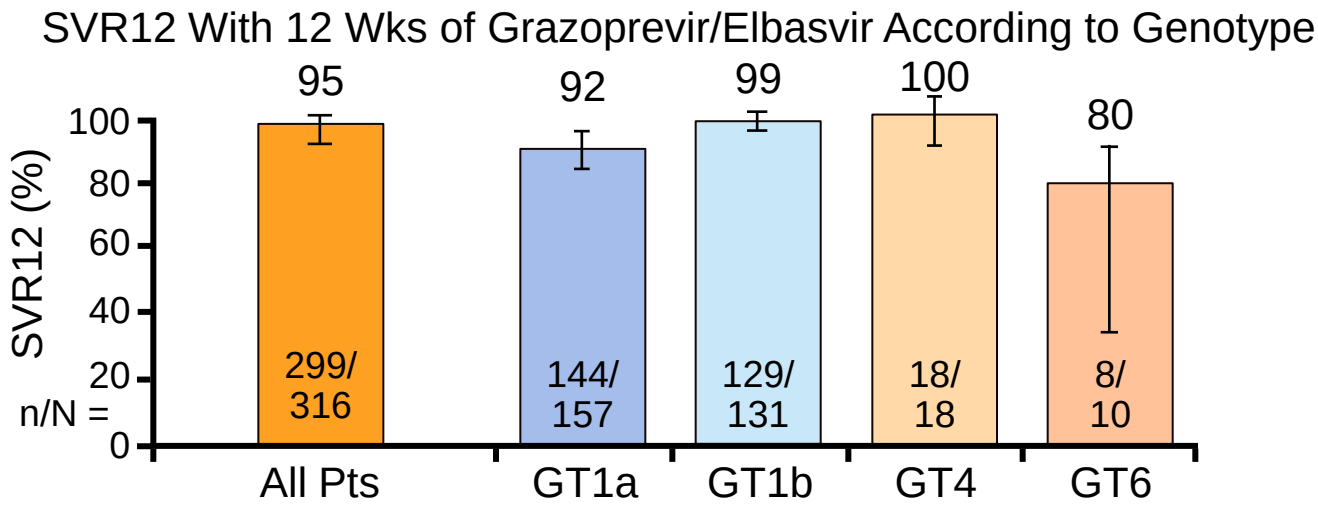
Double-blind
Placebo-controlled
Genotype 1, 4, or 6
Treatment-naïve
Cirrhotics allowed
Primary Endpoint: SVR12

Grazoprevir/elbasvir 100/50 mg daily (FDC)
Baseline demographics:
- Male: 54%
- Mean age: 52.5 years
- Genotype 1a: 50%
- Genotype 4/6: 6%/3%
- Cirrhosis: 22%
- Platelets <100 x 10^3/µL: 8.1%

Grazoprevir, 2nd generation Protease inhibitor
Elbasvir, 2nd generation NS5A inhibitor

Zeuzem S, et al. *J Hepatol.* 2015;62(suppl 2):S213. Abstract G07.

The phase 3 C-EDGE treatment-**naïve** study of 12-week regimen of grazoprevir/elbasvir in patients with chronic HCV genotype 1, 4, or 6 infection. (Zeuzem et al. Abstract G07)



Non-virologic failure	4	3	1	0	0
Breakthrough	1	1	0	0	0
Relapse	12	9	1	0	2

Subgroup analysis: significantly lower SVR12 rates in pts with baseline HCV RNA > 800,000 IU/mL

- No differences according to race, *IL28B* status, presence of cirrhosis

Lower SVR12 rates with baseline NS5A RAVs associated with > 5-fold loss of susceptibility to elbasvir

- Baseline NS5A RAVs (versus no NS5A RAVs): 58% versus 99%
- Baseline NS5A RAVs with ≤5 versus >5-fold potency loss: 90% versus 22%

Zeuzem Z, et al. EASL 2015. Abstract G07

The phase 3 C-EDGE treatment-**naïve** study of 12-week regimen of grazoprevir/elbasvir in patients with chronic HCV genotype 1, 4, or 6 infection. (Zeuzem et al. Abstract G07)

- Grazoprevir/elbasvir generally well tolerated in cirrhotic and noncirrhotic pts
  - No serious treatment-related AEs
  - 1% discontinued medications due to AEs

Adverse Events, %	Noncirrhotic Pts		Cirrhotic Pts	
	GZR/EBV (n = 246)	Pbo (n = 83)	GZR/EBV (n = 70)	Pbo (n = 22)
≥ 1 AE	71	69	54	68
Drug-related AE	39	39	26	41
SAE	3	4	3	0
Drug-related SAE	0	0	0	0
Discontinued for AE	1	0	1	5
Death	< 1	0	1	0

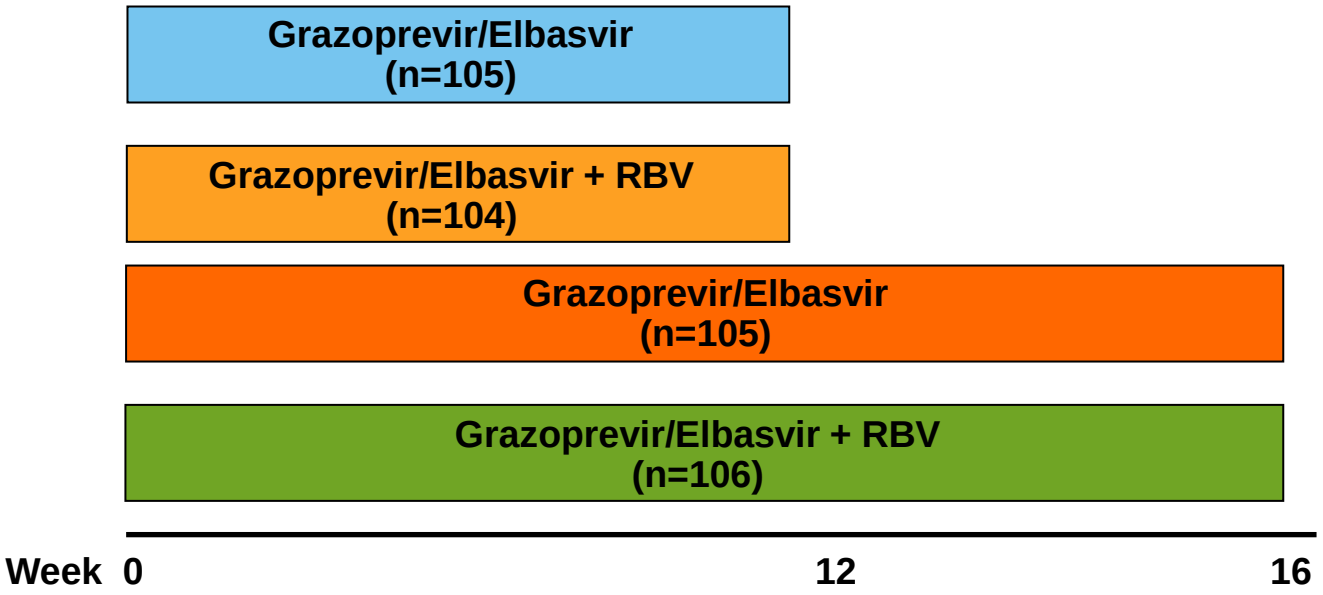
Parameter, %	GZR/EBV (n = 316)	Pbo (n = 105)
Common AEs (> 5%)		
▪ Headache	17	18
▪ Fatigue	16	17
▪ Nausea	9	8
▪ Arthralgia	6	6
Late ALT or AST elevation		
▪ > 2 to 5 x ULN	1.0	3.8
▪ > 5 x ULN	1.3	0
Total bilirubin elevation		
▪ > 2 to 5 x baseline	0.9	0
▪ > 5 x baseline	0.3	0
Decreased hemoglobin		
▪ Grade 1/2	2.9	3.8
▪ Grade 3/4	0	0

Zeuzem Z, et al. EASL 2015. Abstract G07

Efficacy and safety of grazoprevir/elbasvir +/− RBV for 12 weeks in patients with HCV G1 or G4 who previously failed peginterferon/RBV: C-EDGE treatment-**experienced** trial. (Kwo et al. Abstract P0886)

Phase 3

Open-label
Genotype 1, 4, or 6
Prior PR failures
Compensated cirrhosis allowed
HIV allowed
Primary endpoint: SVR12

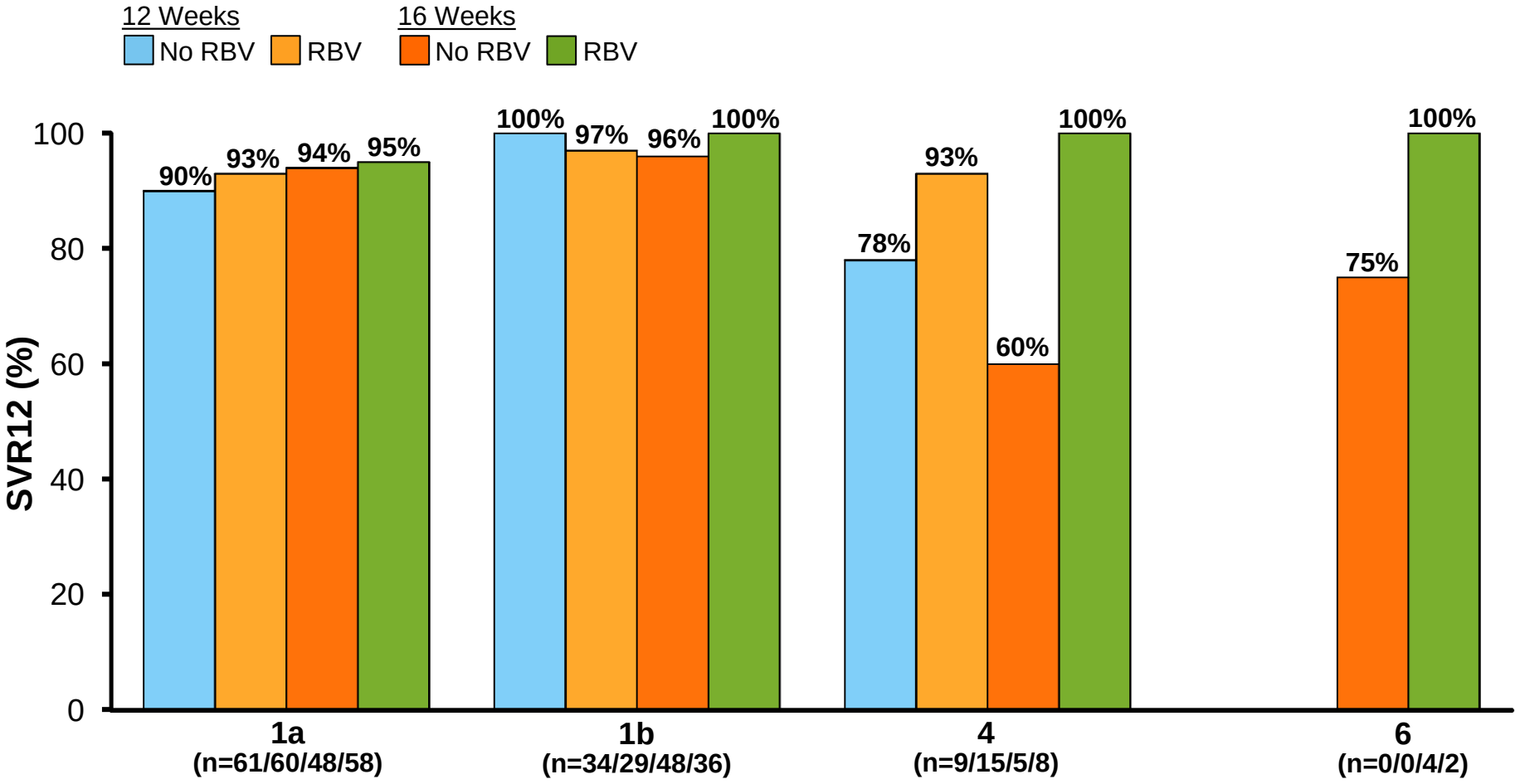


Baseline demographics:
- Male: 60%-69%
- Age: 55-56 years
- Genotype 1a: 46%-58%
- Genotype 4/6: 5%-14%/2%-4%
- HIV coinfection: 4%-6%
- Cirrhosis: 34%-36%

Prior response:
- Null: 41-47%
- Partial: 20-22%
- Relapse: 33-38%

Kwo P, et al. *J Hepatol.* 2015;62(suppl 2):S674. Abstract P0886.

Efficacy and safety of grazoprevir/elbasvir +/− RBV for 12 weeks in patients with HCV G1 or G4 who previously failed peginterferon/RBV: C-EDGE treatment-**experienced** trial. (Kwo et al. Abstract P0886)



PR: pegIFN + RBV.

Kwo P, et al. *J Hepatol.* 2015;62(suppl 2):S674. Abstract P0886.

Efficacy and safety of grazoprevir/elbasvir +/− RBV for 12 weeks in patients with HCV G1 or G4 who previously failed peginterferon/RBV: C-EDGE treatment-**experienced** trial. (Kwo et al. Abstract P0886)

- Lower SVR12 rates only among patients with baseline genotype 1a RAVs that cause >5-fold potency reduction to elbasvir
  - 100% versus 52%
- Genotype 1a with virologic failure (n=12)
  - With baseline NS5A RAV (n=10)
- Relapse
  - 12-week arm (n=12)
  - 16-week arm (n=4)
- Similar safety profile between 12- and 16-week arms
  - RBV-containing arms generally had a higher incidence of adverse events and hemoglobin values <10 g/dL

Kwo P, et al. *J Hepatol.* 2015;62(suppl 2):S674. Abstract P0886.

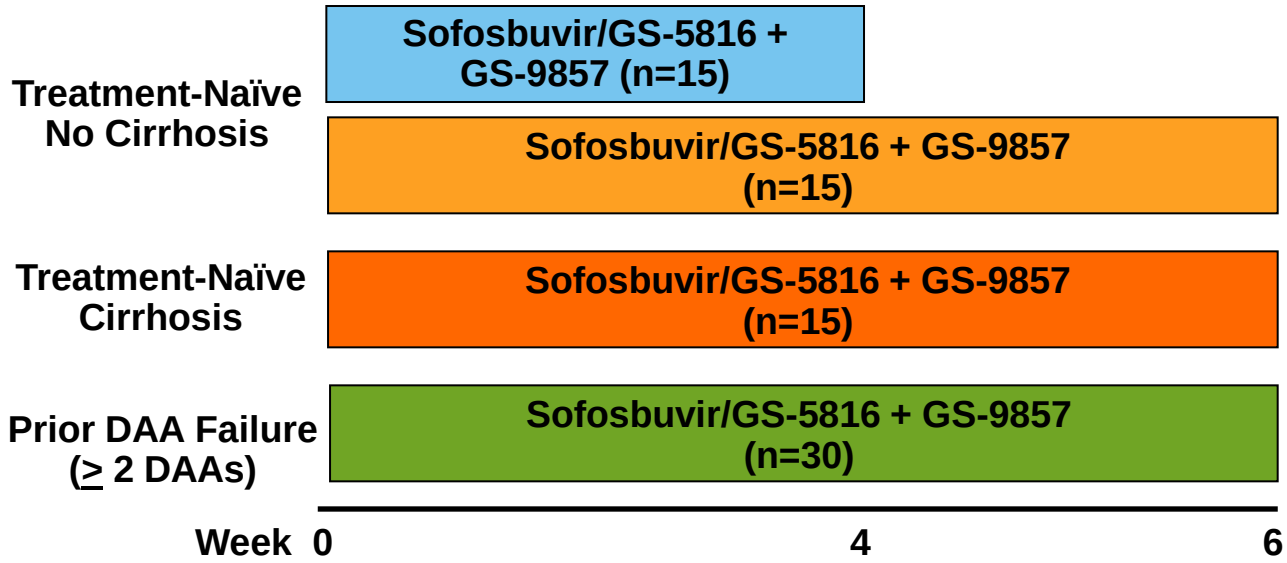
HCV - Future

- What's on the horizon?
- Are these new medications going to allow for shorter therapy?
- What about for patients who have already failed other DAA regimens?

Safety and efficacy of short-duration treatment with GS-9857 combined with sofosbuvir/GS-5816 in treatment-naïve and DAA-experienced genotype 1 patients with and without cirrhosis. (Gane et al. Abstract LP03)

Single-Center

Open-label
Genotype 1
Treatment-naïve and prior DAA failures
Cirrhotics allowed
Primary endpoint: SVR12

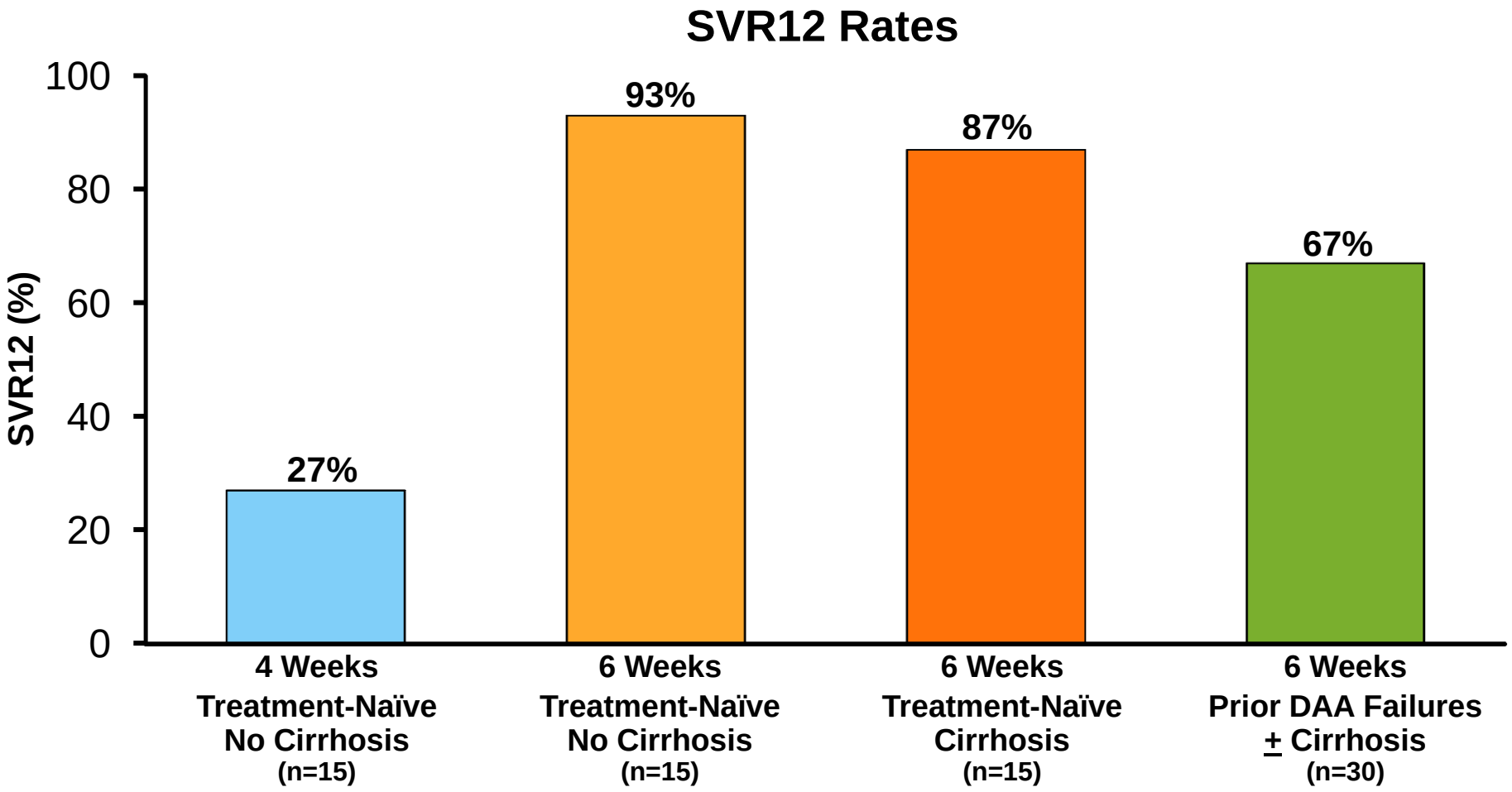


Sofosbuvir/GS-5816 400/100 mg qd + GS-9857 100 mg qd
Baseline demographics:
- Male: 47%-80%
- Mean age: 50-59 years
- White: 80%-93%
- Genotype 1a: 73%-93%
- HCV RNA (log_{10} IU/mL): 6.0-6.3

GS-9857, 2nd generation Protease Inhibitor
GS-5816, 2nd generation NS5A inhibitor

Gane E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP03.

Safety and efficacy of short-duration treatment with GS-9857 combined with sofosbuvir/GS-5816 in treatment-naïve and DAA-experienced genotype 1 patients with and without cirrhosis. (Gane et al. Abstract LP03)



All non-SVR due to relapse, (n=24)

Gane E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP03.

Safety and efficacy of short-duration treatment with GS-9857 combined with sofosbuvir/GS-5816 in treatment-naïve and DAA-experienced genotype 1 patients with and without cirrhosis. (Gane et al. Abstract LP03)

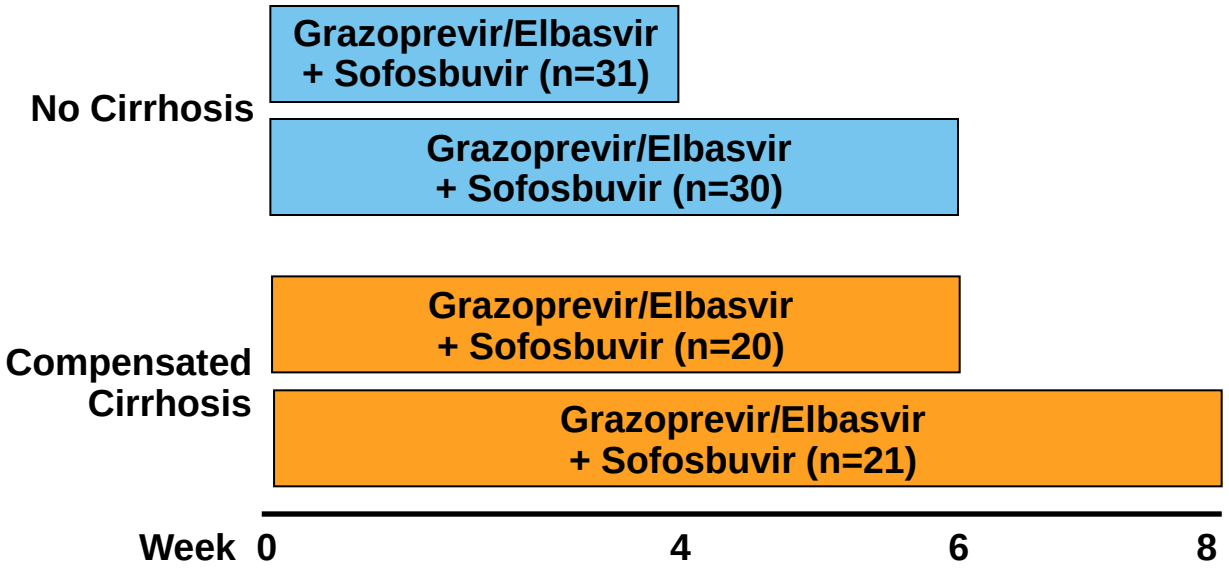
- Relapse (n=24) was not associated with pretreatment RAVs
  - SVR12 with baseline RAVs versus no RAVs
    - Treatment-naïve + cirrhosis: 82% versus 62%
    - Prior DAA failure + cirrhosis: 69% versus 65%
- RAVs were rarely observed at the time of relapse (n=1)
  - Treatment-naïve, cirrhotic: relapse at 6 weeks of therapy, low level V55A
- No multi-DAA class resistance was observed
- Regimens were safe and well tolerated
  - No discontinuations due to adverse events
  - Most common adverse events: nausea, headache, fatigue

Gane E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP03.

C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic, treatment-naive patients with HCV **genotype 1** infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. (Poordad et al. Abstract O006)

Phase 2

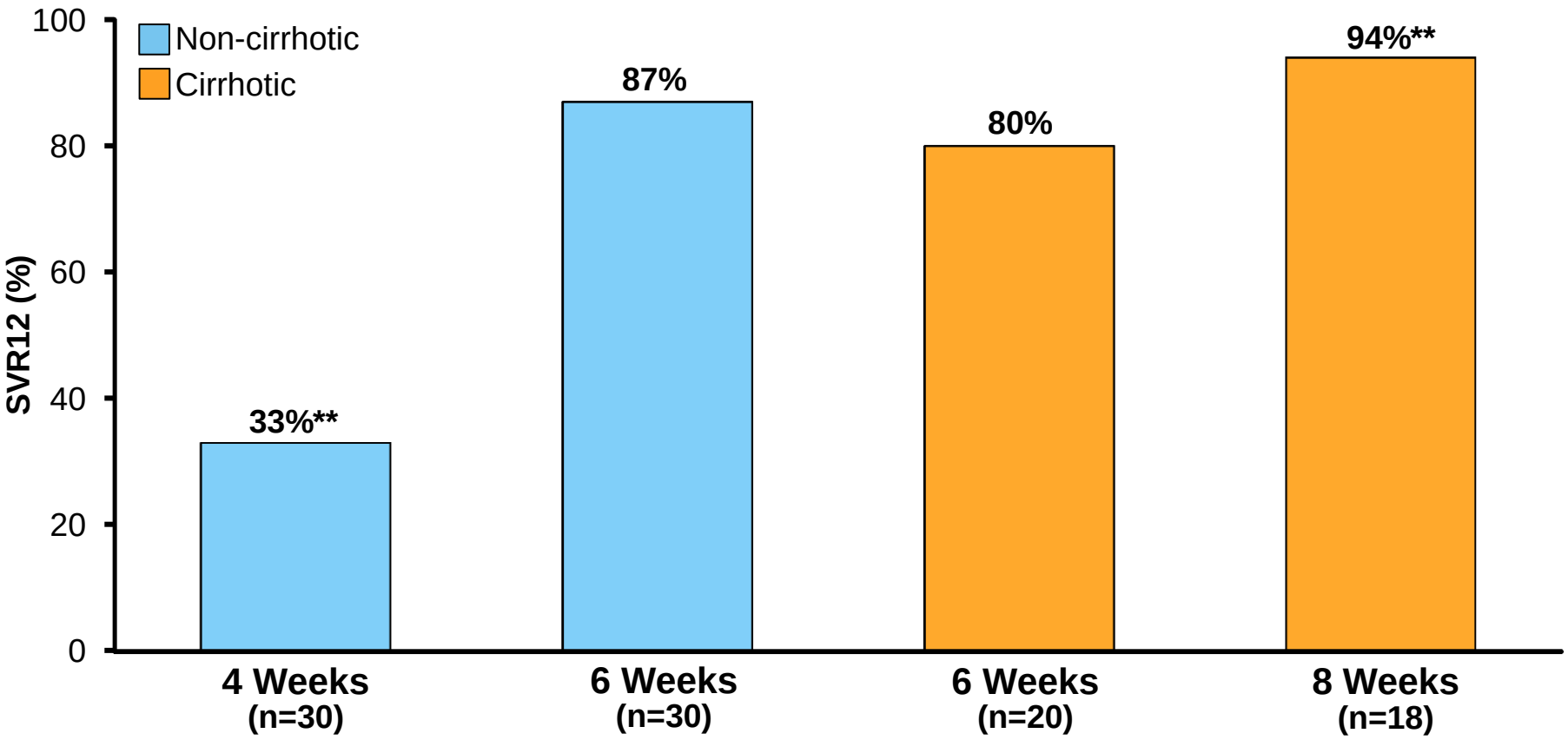
Open-label
Genotype 1
Compensated cirrhosis allowed
Treatment-naïve
Primary endpoint: SVR12*
(*modified ITT)



Grazoprevir/elbasvir 100/50 mg daily + sofosbuvir 400 mg daily
Baseline demographics:
- Male: 66%
- Mean age: 51-57 years
- Genotype 1a: 82%
- Cirrhosis: 43%

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S192-S193. Abstract O006.

C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic, treatment-naive patients with HCV **genotype 1** infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. (Poordad et al. Abstract O006)



**Modified ITT: excludes 1 patient from 4 week arm and 3 patients from 8-week arm with non-virologic discontinuation

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S192-S193. Abstract O006.

C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic, treatment-naive patients with HCV **genotype 1** infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. (Poordad et al. Abstract O006)

- No virologic breakthrough
- Relapse (n=29)
  - 4-week group (n=20)
  - 6-week group (n=8)
  - 8-week group (n=1)
- 9 of 29 relapsers developed NS5A RAVs
  - 6 of 9 patients with NS5A RAVs were in the 4-week arm
- No deaths
- 1 discontinuation due to AE (lymphoma)

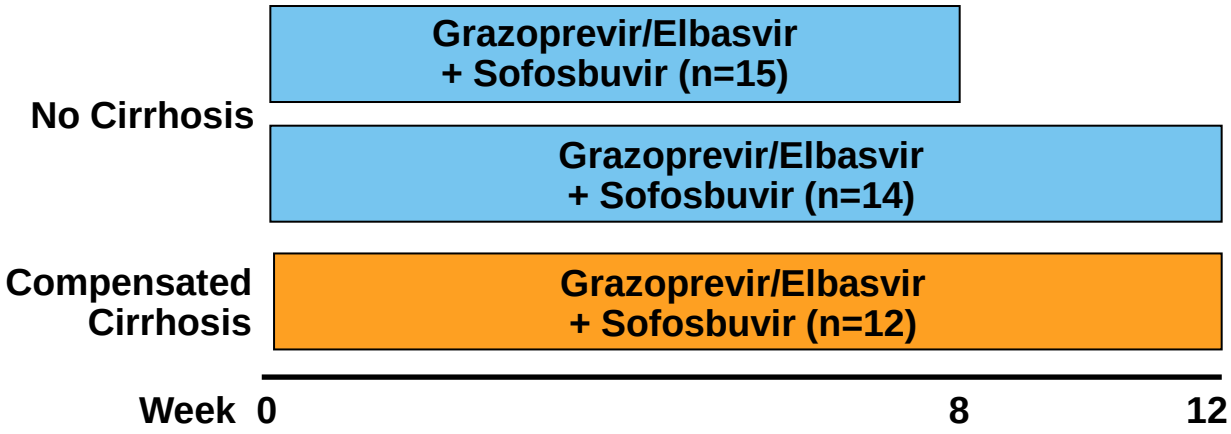
RAV Analysis*

	NS3	NS5A	NS5B
Number of sequences	29	30	30
No RAVs detected (%)	97	60	100
RAVs detected (%)			
Baseline only	0	3.3	0
At treatment failure	3	30	0
Baseline and failure	0	6.7	0

*RAVs conferring >5-fold resistance to component drugs

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S192-S193. Abstract O006.

C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic, treatment-naive patients with HCV genotype 1 infection, for durations of 4, 6 or 8 weeks and **genotype 3** infection for durations of 8 or 12 weeks. (Poordad et al. Abstract O006)



Phase 2

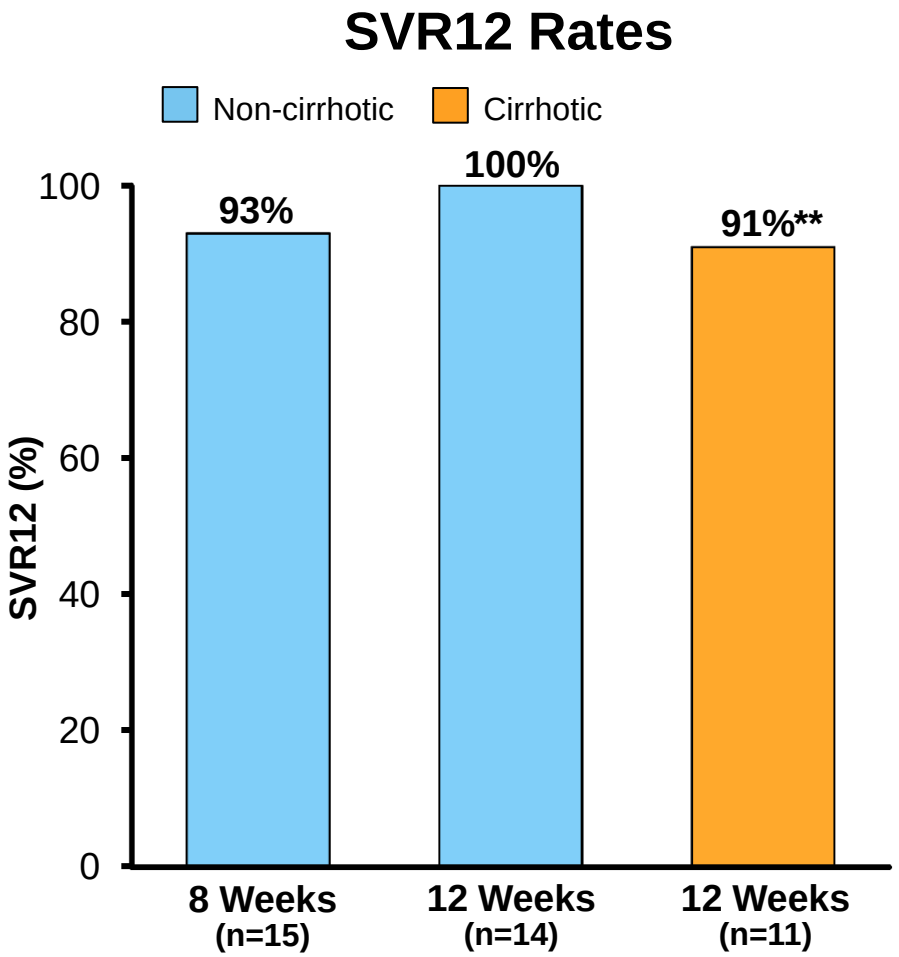
Open-label
Genotype 3
Compensated cirrhosis allowed
Treatment-naïve
Primary endpoint: SVR12*
(*modified ITT)

Grazoprevir/elbasvir 100/50 mg daily + sofosbuvir 400 mg daily
Baseline demographics:
- Male: 57%-83%
- Mean age: 42-55 years

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S192-S193. Abstract O006.

C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic, treatment-naive patients with HCV genotype 1 infection, for durations of 4, 6 or 8 weeks and **genotype 3** infection for durations of 8 or 12 weeks. (Poordad et al. Abstract O006)

- No virologic breakthrough
- Relapse (n=2)
  - 8-week group (n=1)
  - 12-week cirrhotic group (n=1)
- Higher baseline HCV RNA (> 2 million IU/mL) and presence of cirrhosis resulted in lower SVR12 with GT3
- No deaths
- No discontinuations due to AE

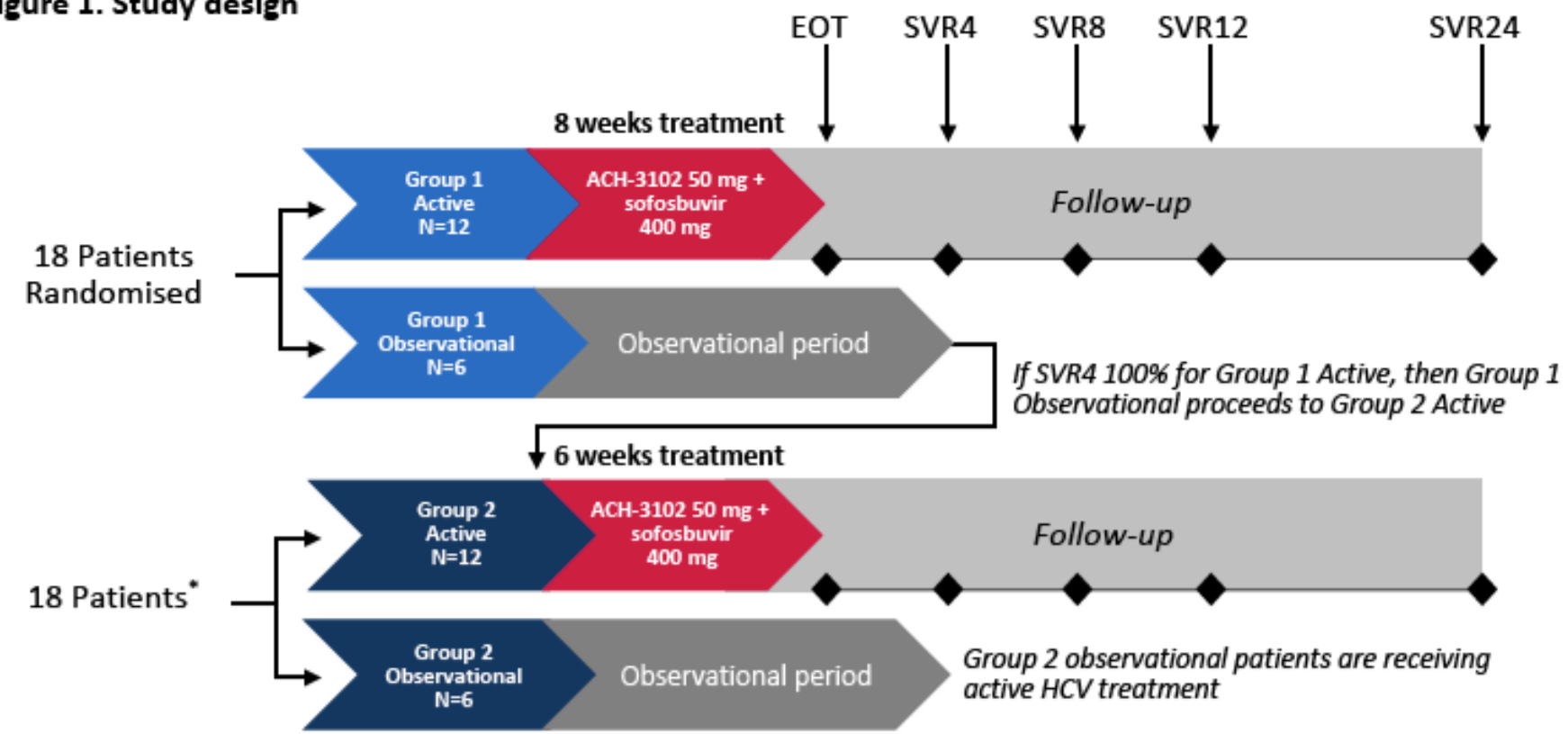


**Modified ITT: excludes 1 patient in cirrhotic arm due to non-virologic failure)

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S192-S193. Abstract O006.

Sustained Virologic Response After ACH-3102 and Sofosbuvir Treatment for 8 or 6 Weeks: a Phase 2 "Proxy" Study (Gane et al. Abstract P017)

Figure 1. Study design

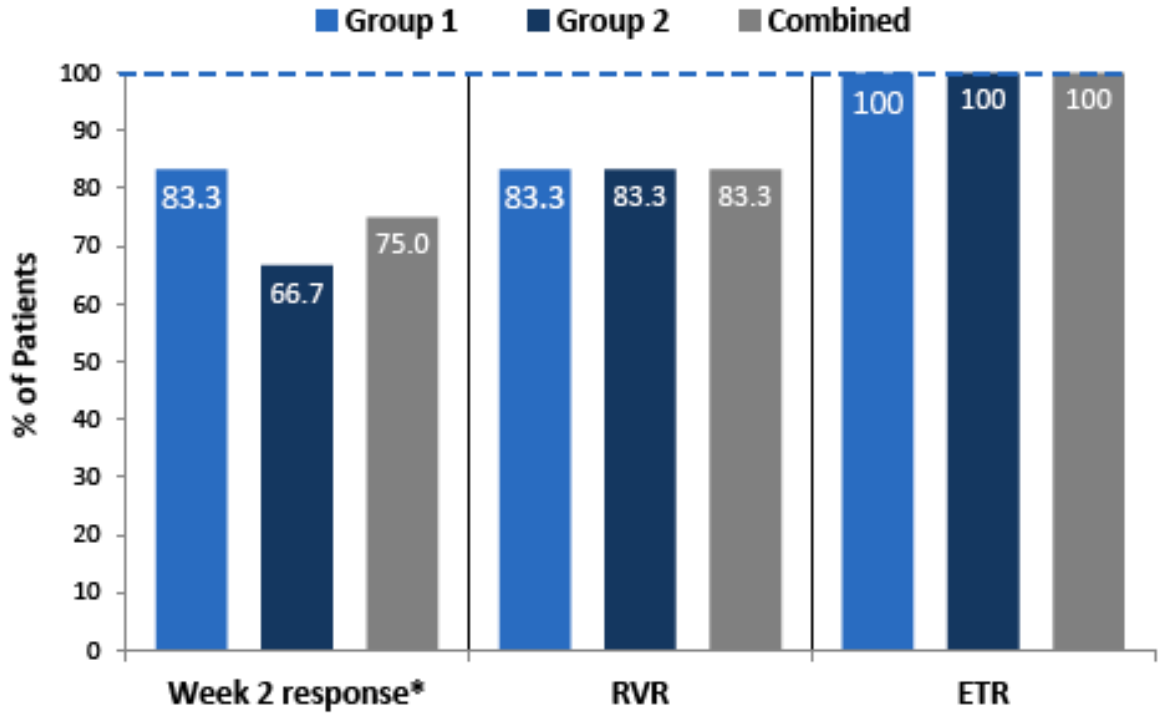


*Six patients from observational Group 1 and 12 patients newly randomised

ACH-3102, 2nd generation NS5A inhibitor

Sustained Virologic Response After ACH-3102 and Sofosbuvir Treatment for 8 or 6 Weeks: a Phase 2 "Proxy" Study (Gane et al. Abstract P017)

Figure 2. Efficacy results for patients who received treatment with ACH-3102 and sofosbuvir (Groups 1 and 2)



Group 1 (8 weeks)
All patients achieved SVR4, SVR12 and SVR24

Group 2 (6 weeks)
All patients achieved SVR 4 and SVR12 (SVR 24 results pending)

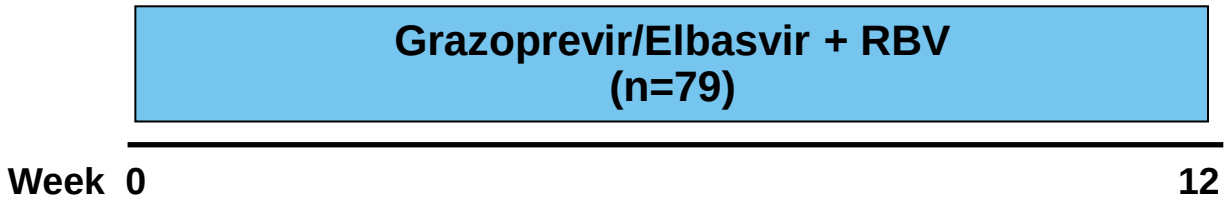
*HCV RNA reported as < $LLOQ_{TD/TND}$; Combined = Group 1 and Group 2; $LLOQ_{TD/TND}$ = lower limit of quantification and target detected or target not detected.

RVR = rapid virologic response; ETR = end of treatment response; SVR4, SVR12 and SVR24 = sustained virologic response at weeks 4, 12 and 24 after end of treatment

HCV - Future

- What's on the horizon?
- Are these new medications going to allow for shorter therapy?
- What about for patients who have already failed other DAA regimens?

C-SALVAGE: Grazoprevir, elbasvir and ribavirin for chronic HCV-genotype 1 infection after failure of direct-acting antiviral therapy. Forns et al. Abstract O001; J Hepatol 2015;Apr 17)



Phase 2

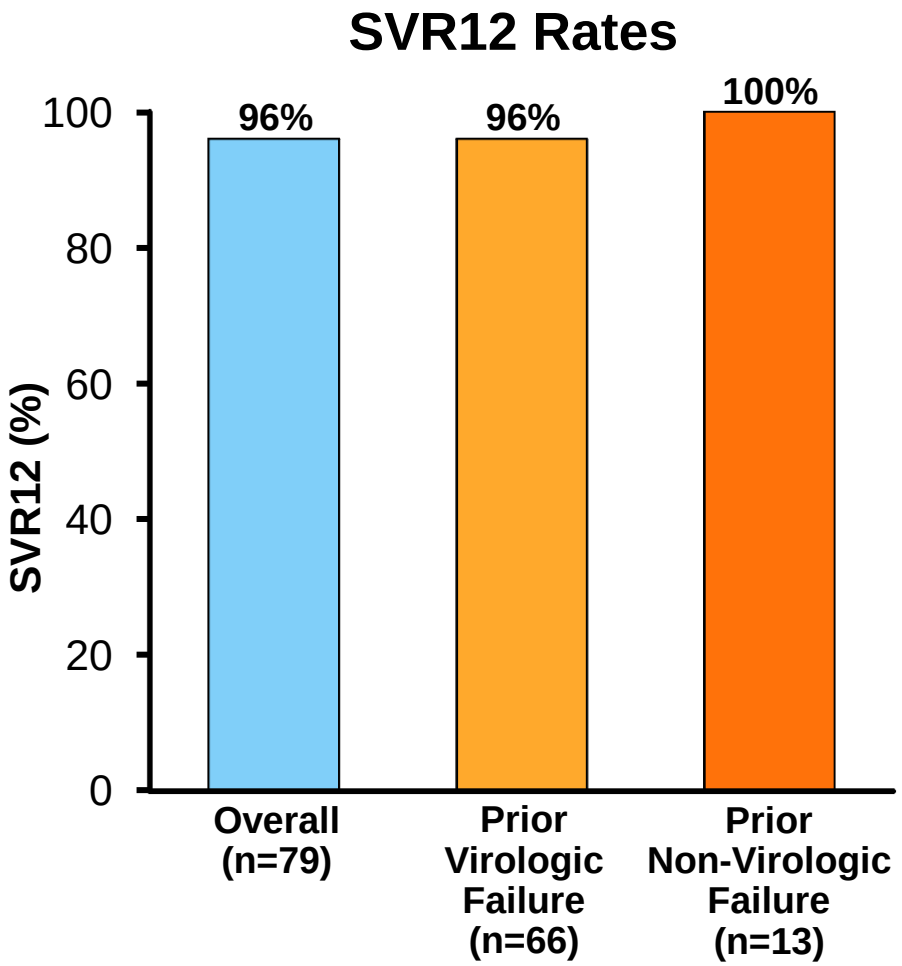
Open-label
Genotype 1
Failed >4 weeks of triple therapy (PR plus either boceprevir, telaprevir, simeprevir)
Compensated cirrhosis allowed
Primary endpoint: SVR12

Grazoprevir/elbasvir 100/50 mg daily
Baseline demographics:
- Male: 58%
- Mean age: 54 years
- Genotype 1a: 38%
- Cirrhosis: 43%
- Past history of virologic failure: 84%
  - Boceprevir: 35%
  - Telaprevir: 54%
  - Simeprevir: 10%
- Past history of intolerance: 15%

Forns X, et al. *J Hepatol.* 2015;62(suppl 2):S190. Abstract O001.
Forns X, et al. *J Hepatol.* 2015;Apr 17. [Epub ahead of print].

C-SALVAGE: Grazoprevir, elbasvir and ribavirin for chronic HCV-genotype 1 infection after failure of direct-acting antiviral therapy. Forns et al. Abstract O001; J Hepatol 2015;Apr 17)

- Baseline RAVs:
  - NS3: 43.6% [SVR in 31 of 34 (91%)]
  - NS5A: 10.1% [SVR in 6 of 8 (75%)]
  - NS3 + NS5A: 7.6% [SVR in 4 of 6 (66.7%)]
- Relapse (n=3)
  - Genotype 1a (n=2), 1b (n=1)
  - 2 of 3 had baseline RAVs at both NS3 and NS5A
- RAVs at relapse (n=3)
  - A156T, M28T, Q30H, Y93H
  - A156T, Y93H
  - A156T, Q30R
- Safety
  - Generally well tolerated
  - Discontinuations due to AE (n=1)
  - No serious drug-related AEs

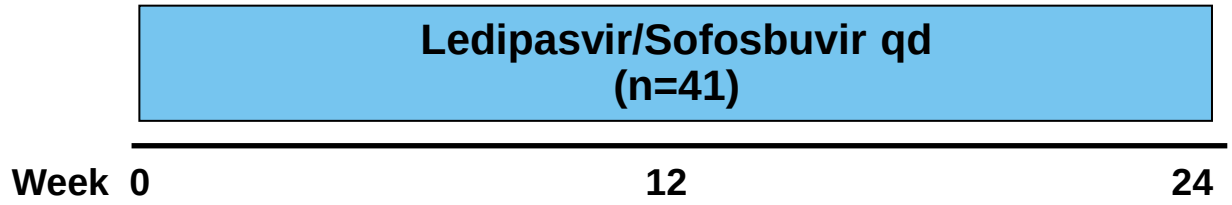


Forns X, et al. *J Hepatol.* 2015;62(suppl 2):S190. Abstract O001.
Forns X, et al. *J Hepatol.* 2015;Apr 17. [Epub ahead of print].

HCV Retreatment

- What should I do for my patient who relapsed after taking Sofosbuvir/Ledipasvir for 8 or 12 weeks?

Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks (E. Lawitz et al. Abstract O005)



Phase 2

Open-label study
Prior failures of 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens
All Genotype 1
Primary endpoint: SVR12

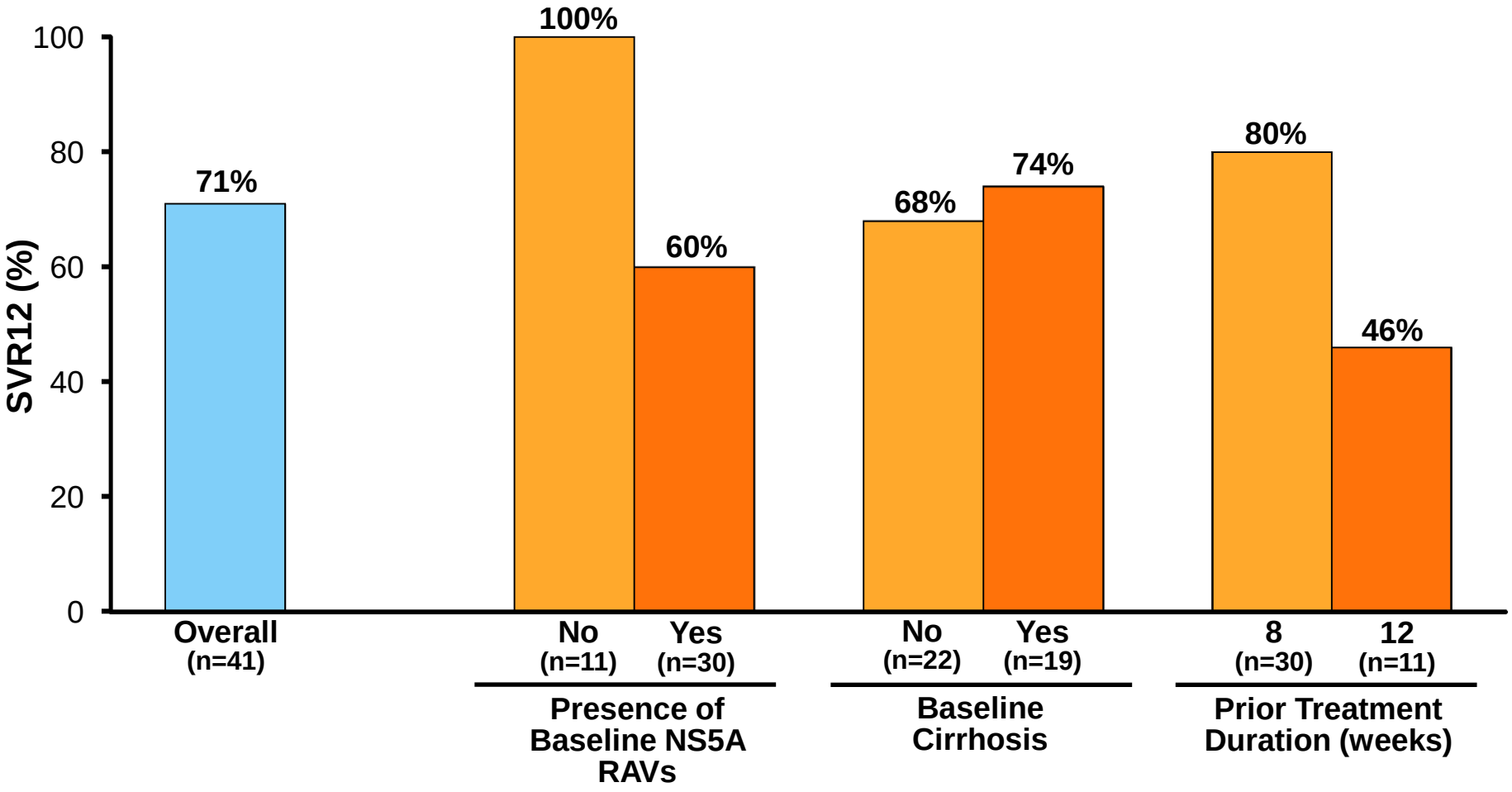
Ledipasvir/sofosbuvir 90/400 mg daily
No ribavirin
Baseline demographics:
- Male: 83%
- Mean age: 58 years
- Genotype 1a: 83%
- HCV RNA (log_{10} IU/mL): 6.2
- Cirrhosis: 46%

Prior HCV treatment duration:
- 8 weeks (73%, 63% with NS5A RAVs)
- 12 weeks (27%, 100% with NS5A RAVs)

Lawitz E, et al. *J Hepatol.* 2015;62(suppl 2):S192. Abstract O005.

RAV, resistance-associated variant

Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks (E. Lawitz et al. Abstract O005)



Lawitz E, et al. *J Hepatol.* 2015;62(suppl 2):S192. Abstract O005.

Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks (E. Lawitz et al. Abstract O005)

- Baseline NS5A RAVs
  - Associated with virologic failure
  - More likely to develop with longer duration of prior ledipasvir/sofosbuvir treatment
- At baseline, no NS5B resistance-associated (S282T) or treatment-emergent (L159F, V321A) variants were detected
- At virologic failure, NS5B variants detected in 4 of 12 patients
  - S282T (n=2), L159F (n=1)
  - S282T + L159F (n=1)
- Safety
  - No new safety signals

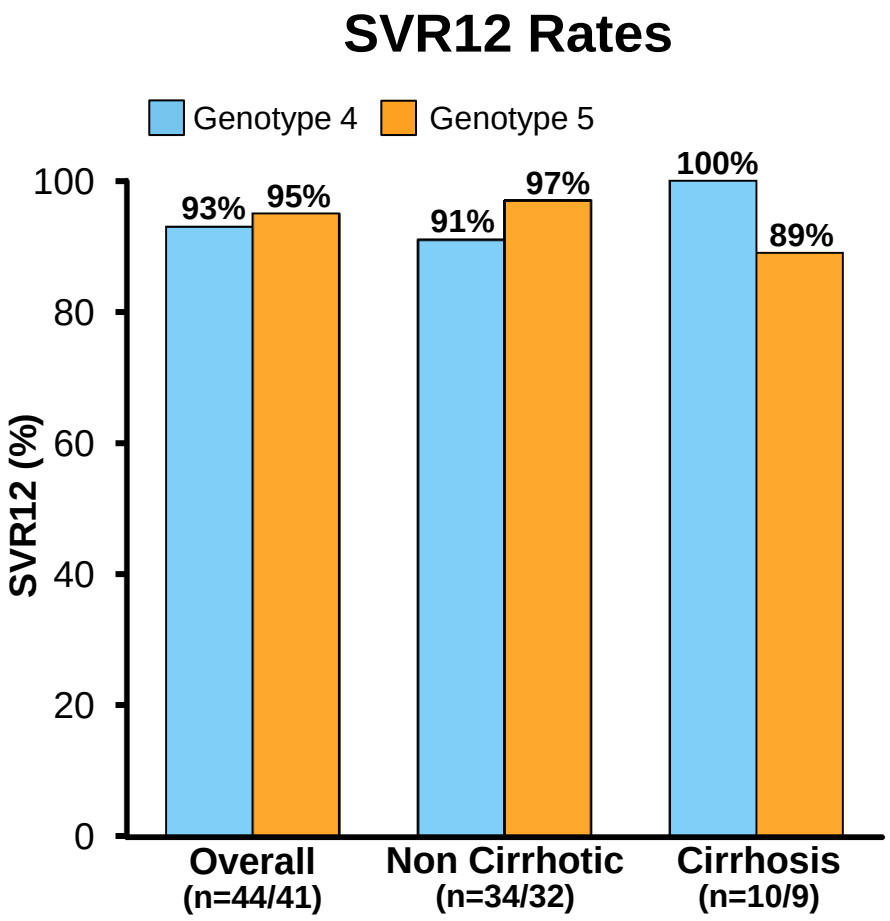
Lawitz E, et al. *J Hepatol.* 2015;62(suppl 2):S192. Abstract O005.

HCV – Other genotypes

- What should I do for my patient with an unusual genotype?

Ledipasvir/sofosbuvir treatment results in high SVR rates in patients with chronic genotype 4 and 5 HCV infection. (Abergel et al. Abstract O056)

- Open-label study (France)
  - Treatment-naïve or -experienced
  - Ledipasvir/sofosbuvir for **12 weeks**
- SVR12 rates similar regardless of treatment experience and/or cirrhosis
  - All treatment failures due to relapse
- RAVs
  - Baseline NS5A RAVs did not impact SVR12
  - No NS5B RAVs at baseline
  - At failure:
    - Y93C + S282T (n=1, genotype 4)
    - S282T (n=1, genotype 5)
- Safety
  - Well tolerated and no new safety signals

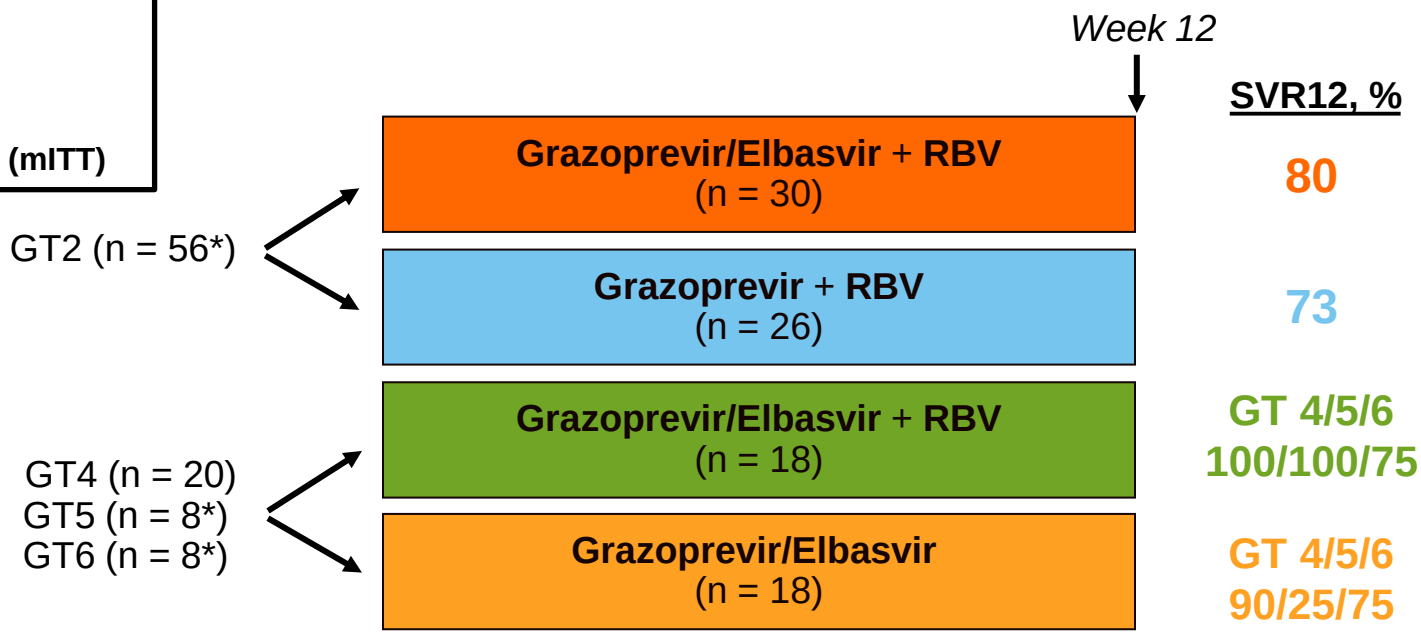


Abergel A, et al. *J Hepatol.* 2015;62(suppl 2):S219. Abstract O056.

C-SCAPE: Efficacy and Safety of 12 weeks of Grazoprevir +/- Elbasvir +/- RBV in patients With HCV GT2, 4, 5, or 6 infection. (Brown et al. Abstract P0771).

Phase 2

Open-label, randomized
Genotypes 2/4/5/6
Non-cirrhotic
Treatment-naïve
Primary endpoint: SVR12 (mITT)



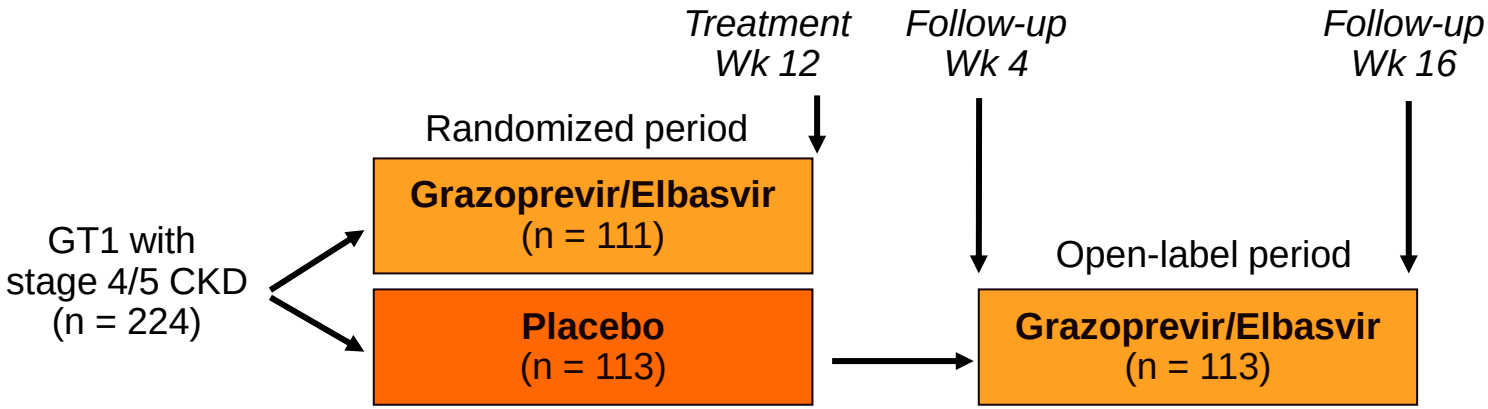
*mITT population: 6 pts excluded due to improper genotyping. Grazoprevir dosed 100 mg orally once daily; elbasvir dosed 50 mg orally once daily; RBV dosed at 800-1400 mg/day based on weight.

- Efficacy reduced in pts with GT2 with baseline HCV RNA > 2 million IU/mL
- Grazoprevir/elbasvir appears active in GT5 (+RBV) and GT6, although numbers were small

HCV – Chronic Kidney Disease

- Anything new for this underserved group?

C-SURFER: Grazoprevir plus Elbasvir in treatment-naïve and treatment-experienced patients with HCV genotype 1 and Chronic Kidney Disease. (Roth et al. Abstract LP02)



(Also included a PK analysis substudy with 11 additional patients)

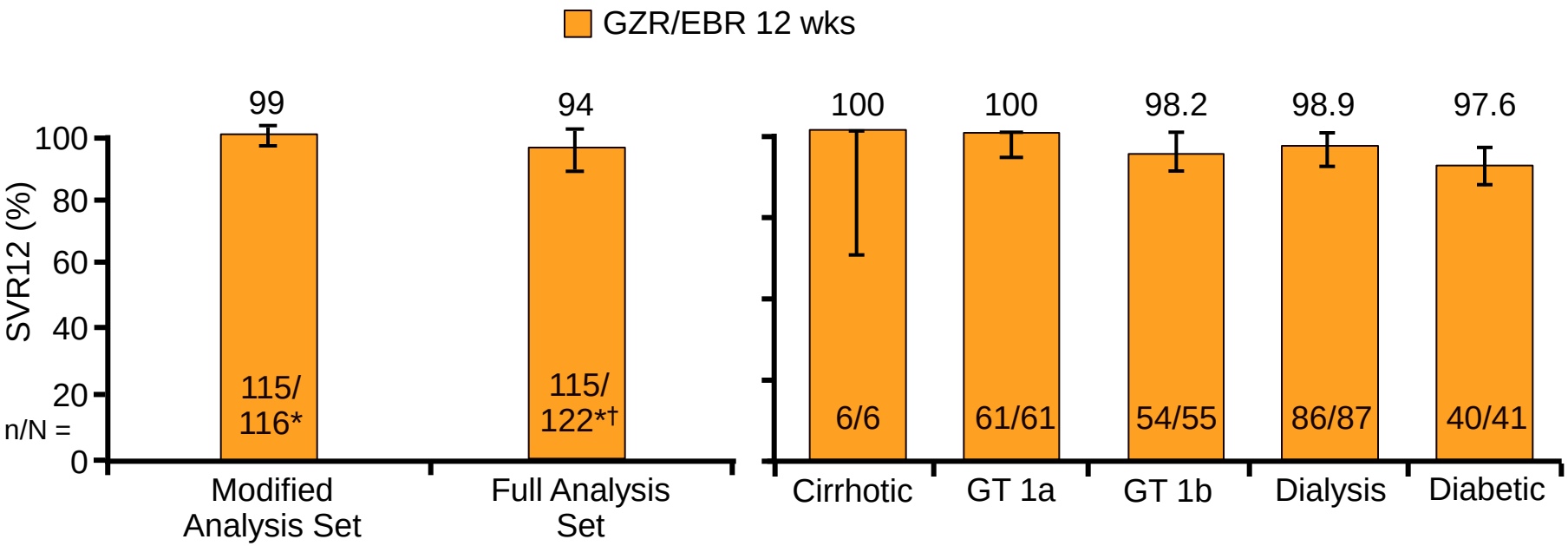
Phase 3

Part randomized, parallel-group
Placebo-controlled
Genotype 1
Cirrhotics allowed
Treatment-naïve or -experienced
Primary endpoint: SVR12*
(*modified ITT)

Grazoprevir/elbasvir 100/50 mg daily (FDC)
Baseline demographics:
- Male: 73%
- GT1a: 52%
- Cirrhosis: n=6
- CKD stage 4: 19%
- CKD stage 5: 81% (76% on dialysis)
- Diabetes: 34%

CKD stage 4 CrCl <30 mL/min
CKD stage 5 CrCl<15 mL/min or HD

C-SURFER: Grazoprevir plus Elbasvir in treatment-naïve and treatment-experienced patients with HCV genotype 1 and Chronic Kidney Disease. (Roth et al. Abstract LP02)



Modified analysis set: PK substudy and patients randomized to immediate treatment who received ≥ 1 drug dose; excludes patients who died or discontinued unrelated to study treatment.
Full analysis set: all pts receiving ≥ 1 drug dose: (n=11) PK substudy; (n=111) immediate treatment arm.
*1 pt relapsed on each arm.
†6 pts in the full analysis set discontinued unrelated to treatment: lost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).

C-SURFER: Grazoprevir plus Elbasvir in treatment-naïve and treatment-experienced patients with HCV genotype 1 and Chronic Kidney Disease. (Roth et al. Abstract LP02)

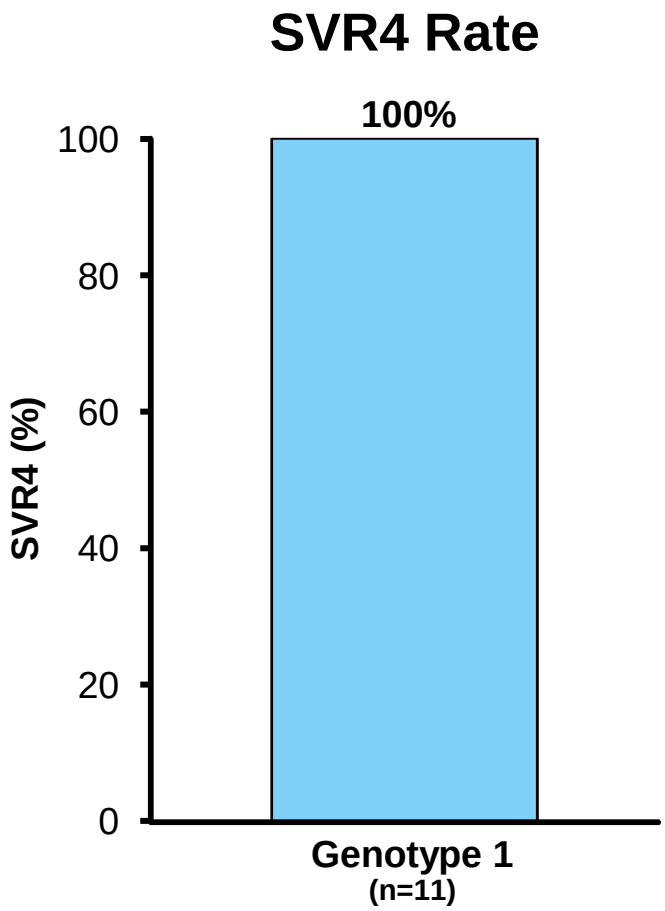
Adverse Events, %	Grazoprevir/Elbasvir (Randomized Treatment) (n = 111)	Placebo (n = 113)
Serious AEs	14.4	16.8
Discontinuation due to AE	0	4.4
Death	0.9	2.7
Common AEs*	75.7	84.1
▪ Headache	17.1	16.8
▪ Nausea	15.3	15.9
▪ Fatigue	9.9	15.0
▪ Insomnia	6.3	10.6
▪ Dizziness	5.4	15.9
▪ Diarrhea	5.4	13.3
Hb grade decrease from baseline		
▪ 1 grade	24.3	26.5
▪ 2 grades	12.6	7.1
▪ 3 grades	3.6	1.8
▪ 4 grades	0	0.9

*Reported in ≥ 10% of pts in either arm.

Roth D, et al. EASL 2015. Abstract LP02

Safety of ombitasvir/paritaprevir/ritonavir plus dasabuvir for treating HCV GT1 infection in patients with severe renal impairment or end-stage renal disease: the RUBY-I study. (Pockros et al. Abstract L01)

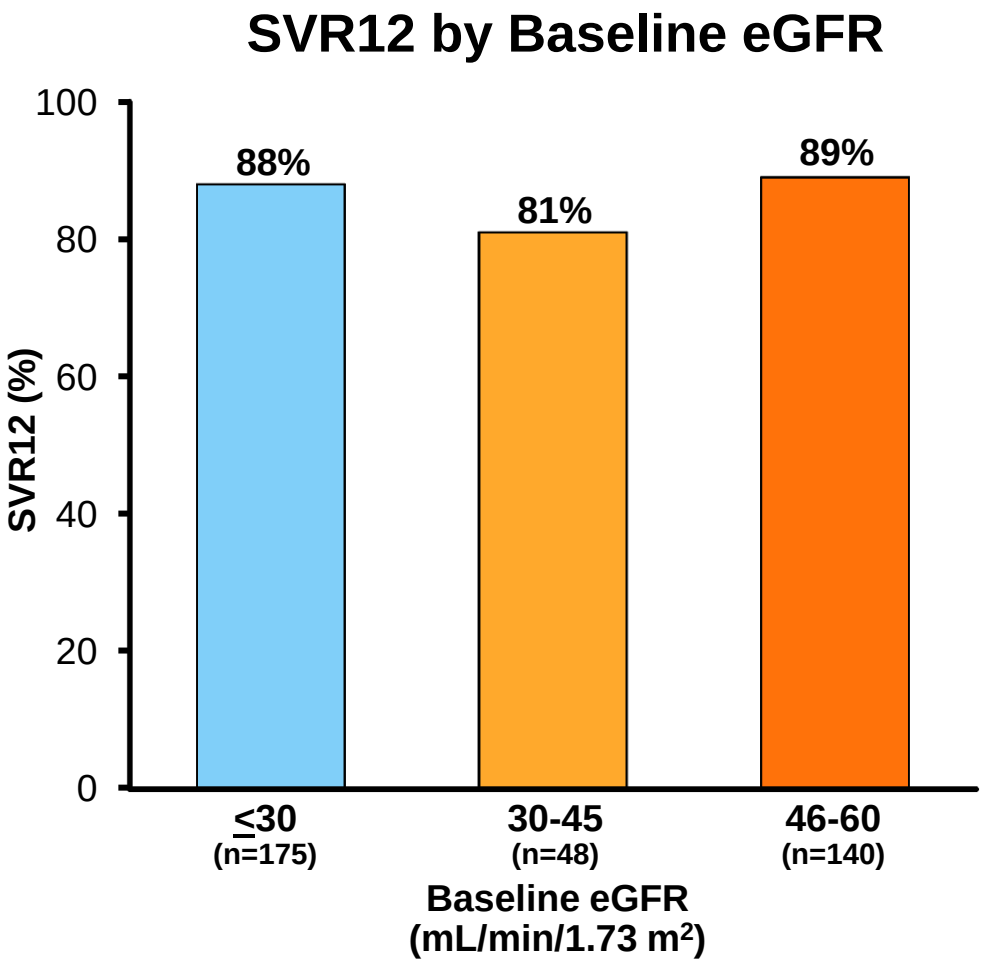
- Non-cirrhotic HCV genotype 1
  - eGFR: <30 mL/min/1.73 m^2
  - Hemoglobin ≥10 g/dL
  - Black/Hispanic: 85%
- Ombitasvir/paritaprevir/r + dasabuvir
  - Genotype 1a with RBV, genotype 1b w/o RBV
- Primary outcome: SVR12
  - Interim SVR4 analysis (n=11)
- Safety (n=13)
  - No discontinuations due to adverse events
  - Hemoglobin reductions were managed with monitoring and RBV dose interruption (for 8/13 patients) and erythropoietin administration (for 4/13 patients)



Pockros PJ, et al. *J Hepatol.* 2015;62(suppl 2):S257. Abstract L01.

Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCV-TARGET. (Saxena et al. Abstract LP08)

- Real-world experience
- HCV genotypes 1, 2, 3, 4, 5, 6
  - Treatment-naïve and experienced
  - Cirrhotics allowed
- Sofosbuvir regimens
  - Sofosbuvir + RBV
  - Sofosbuvir + simeprevir ± RBV
  - Sofosbuvir + PR
- Primary outcome: SVR12



PR: pegIFN + RBV.

Saxena V GR, et al. *J Hepatol.* 2015;62(suppl 2):S259. Abstract LP08.

Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCV-TARGET. (Saxena et al. Abstract LP08)

n (%)	eGFR ≤ 30 (N=10)	eGFR 31–45 (N=29)	eGFR 46–60 (N=78)	eGFR>60 (N=601)
Common AEs Fatigue Headache Nausea	3 (30) 1 (10) 2 (20)	6 (21) 3 (10) 3 (10)	21 (27) 11 (14) 15 (19)	146 (24) 97 (16) 72 (12)
Anemia requiring Transfusion(s)	1 (10)	2 (7)	1 (1)	5 (1)
Worsening Renal Function	2 (20)	2 (7)	3 (4)	6 (1)
Renal or Urinary System AEs	2 (20)	2 (7)	6 (8)	19 (3)
Serious AEs	2 (20)	5 (17)	4 (5)	30 (5)
Early Treatment D/C	1 (10)	2 (6)	4 (5)	13 (2)
Death	1 (10)	0 (0)	2 (3)	3 (<0.5)

- Patients with reduced baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and SAEs during therapy
- D/C from AEs were similar across all ranges of renal function

Saxena, EASL, 2015, LP08

Safety and Efficacy of Sofosbuvir + Simeprevir without RBV in HCV GT1 patients with ESRD or GFR < 30 mL/min. (Nazario et al. Abstract P0802)

SOF 400 mg + SMV 150 mg once daily for 12 weeks*

Baseline Demographics

	All patients n=17
Median age, y (range)	57 (46–69)
Male, n (%)	14 (82)
African American, n (%)	12 (71)
HCV GT 1a, n (%)	13 (76)
HCV RNA level > 800,000 IU/mL, n (%)	13 (76)
Patients on dialysis, n (%)	15 (88)
Patients with GFR < 30 mL/min; not on dialysis, n (%)	2 (12)
Fibrosis score, n (%)	
F3	4 (24)
F4	8 (47)
Treatment experienced, n (%)	3 (18)

AEs on Treatment

	All patients n=17
Any, n (%)	4 (24)
Nausea, n (%)	1 (5)
Headache, n (%)	1 (5)
Insomnia, n (%)	2 (12)
Anemia (≥ 2 g/dL decrease in Hgb), n (%)	1 (5)

- No D/C of therapy due to AE
- No hospitalizations due to therapy
- No issues on dialysis related to therapy

All 11 (100%) patients who have completed treatment achieved SVR12

*All patients were made aware of and consented for off-label use of SOF+SMV

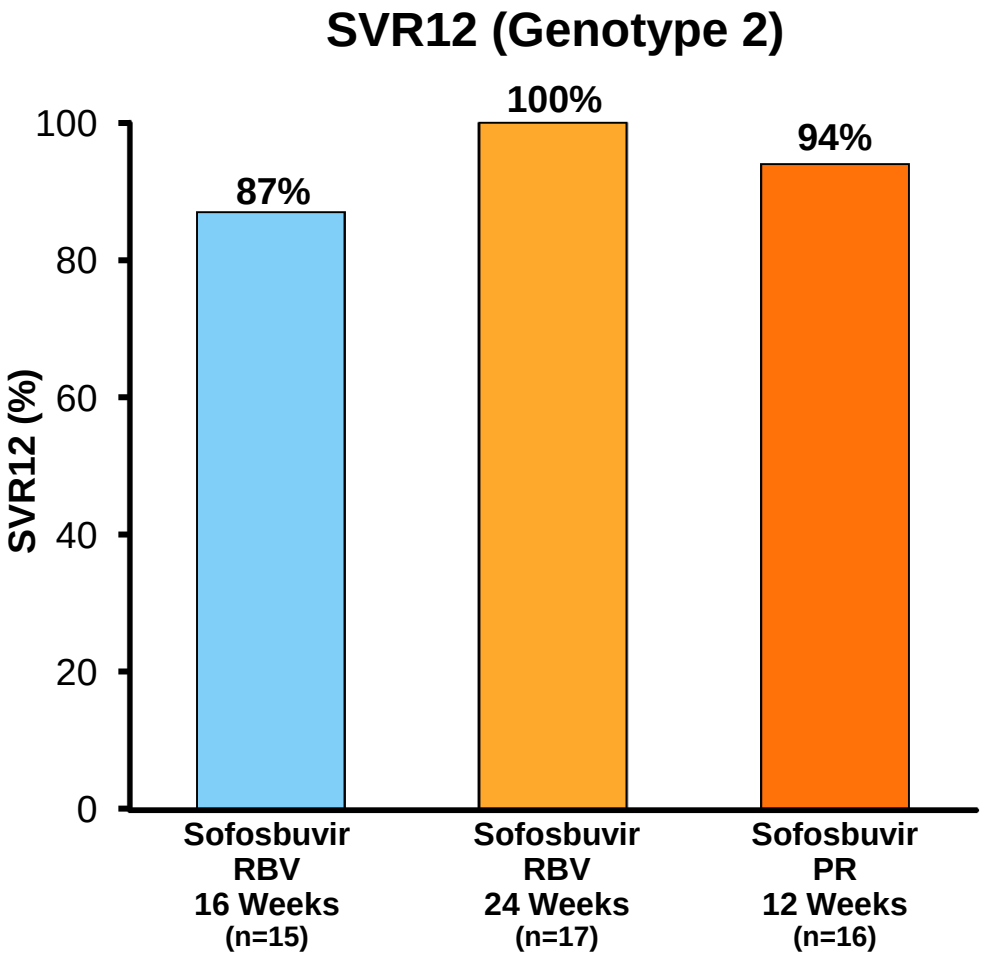
Nazario, EASL, 2015, P0802

HCV – Genotype 3

- What about the new “hardest to treat genotype”?

Sofosbuvir + peginterferon/ribavirin for 12 weeks vs sofosbuvir + ribavirin for 16 or 24 weeks in genotype 3 HCV infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: the BOSON study. (Foster et al. Abstract L05)

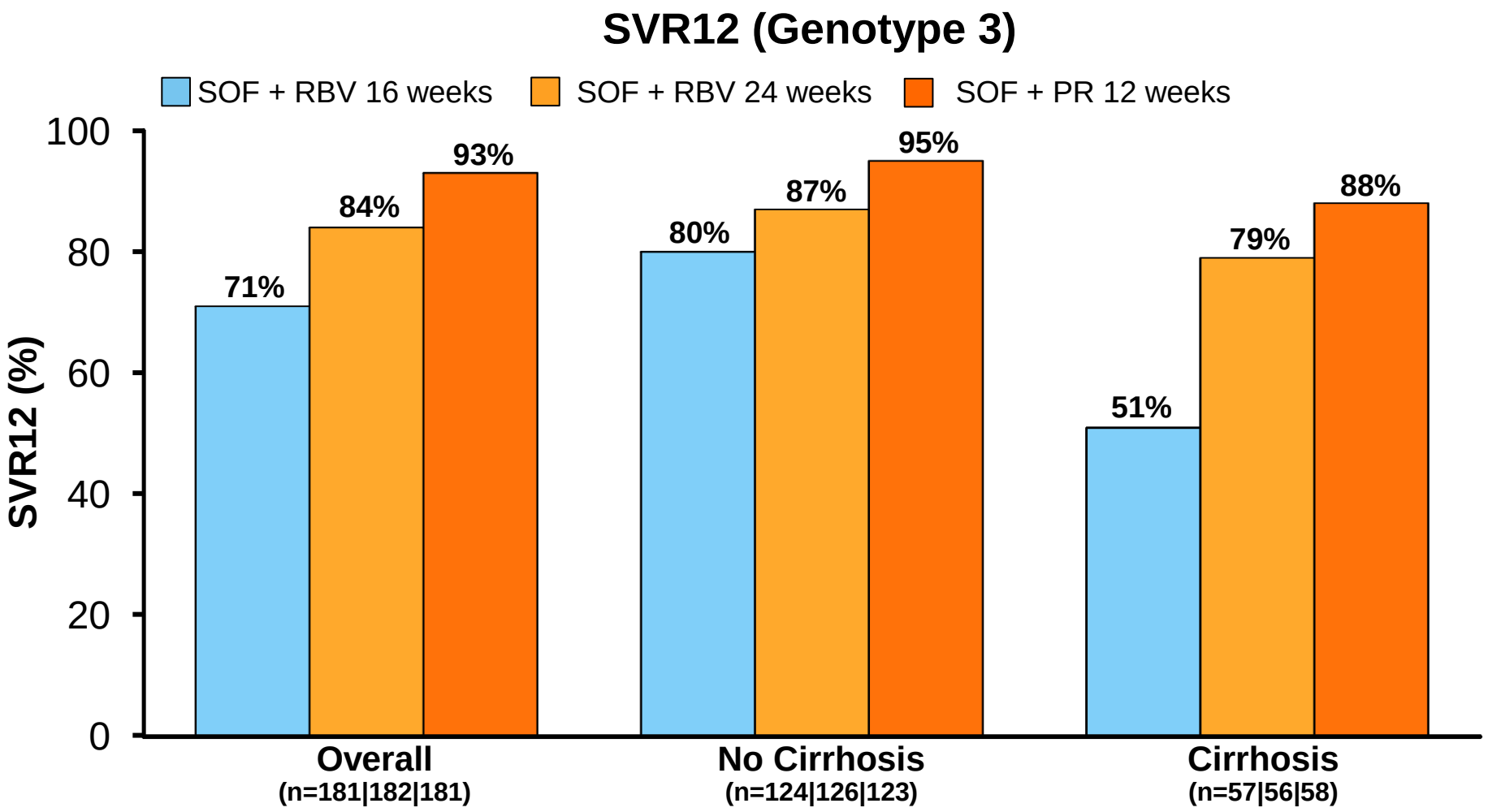
- Open-label study
  - Genotype 2
    - Treatment-experienced (100%)
    - Cirrhosis (100%)
  - Genotype 3
    - Treatment-naïve or experienced
    - With or without cirrhosis
  - Platelets >60,000 cells/mm^3
- Primary outcome: SVR12



PR: pegIFN + RBV.

Foster GR, et al. *J Hepatol.* 2015;62(suppl 2):S259. Abstract L05.

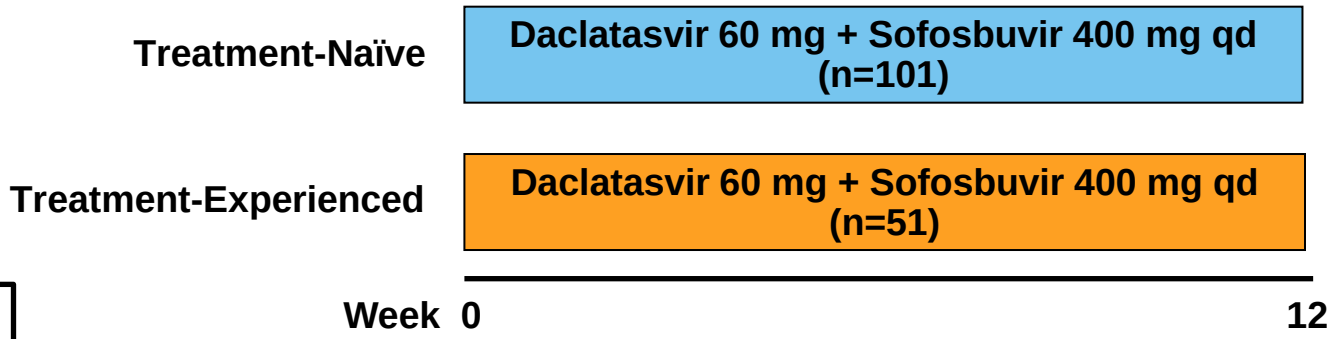
Sofosbuvir + peginterferon/ribavirin for 12 weeks vs sofosbuvir + ribavirin for 16 or 24 weeks in genotype 3 HCV infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: the BOSON study. (Foster et al. Abstract L05)



SOF: sofosbuvir; PR: pegIFN + RBV.

Foster GR, et al. *J Hepatol.* 2015;62(suppl 2):S259. Abstract L05.

All-oral 12-week combination treatment with daclatasvir and sofosbuvir in treatment-experienced patients infected with HCV genotype 3: a sub-analysis of the ALLY-3 phase 3 study. (Nelson et al. Abstract P0782)



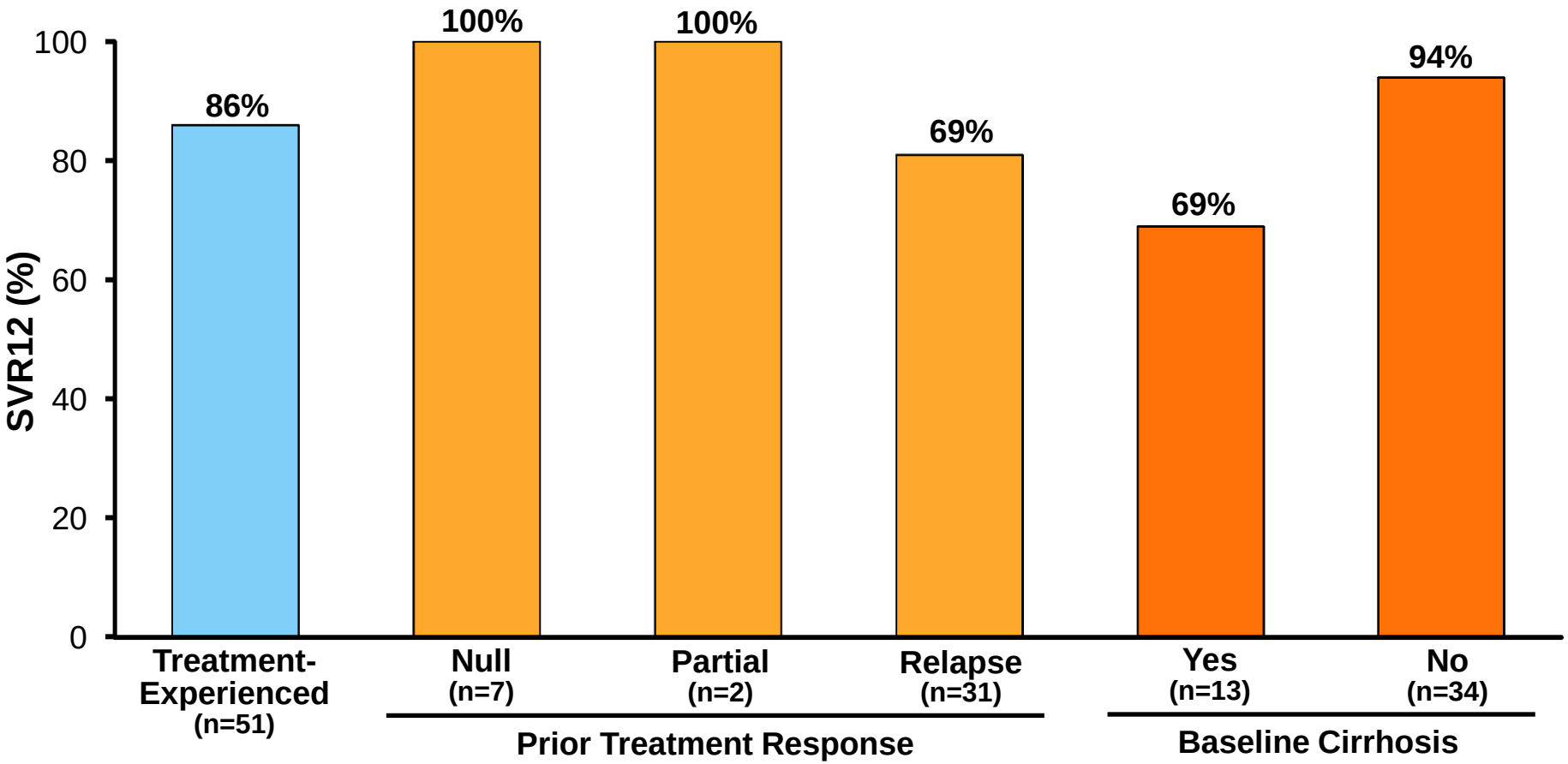
Phase 3

Open-label
Genotype 3
Treatment-naïve and experienced
Cirrhosis allowed
Primary endpoint: SVR12

Previous sofosbuvir or alisporivir failures included
Baseline demographics:
- Male: 57%-63%
- Mean age: 53-58 years
- White: 88%-91%
- HCV RNA >800K IU/mL: 69%-75%
- Cirrhosis: 19%-25%.

Nelson D, et al. *J Hepatol.* 2015;62(suppl 2):S624. Abstract P0782.

All-oral 12-week combination treatment with daclatasvir and sofosbuvir in treatment-experienced patients infected with HCV genotype 3: a sub-analysis of the ALLY-3 phase 3 study. (Nelson et al. Abstract P0782)



SVR12 by prior regimen: IFN (88%), sofosbuvir (71%), alisporivir (100%).

For TN group SVR12:
90% overall; 58% for cirrhotics
(Hepatology 2015)

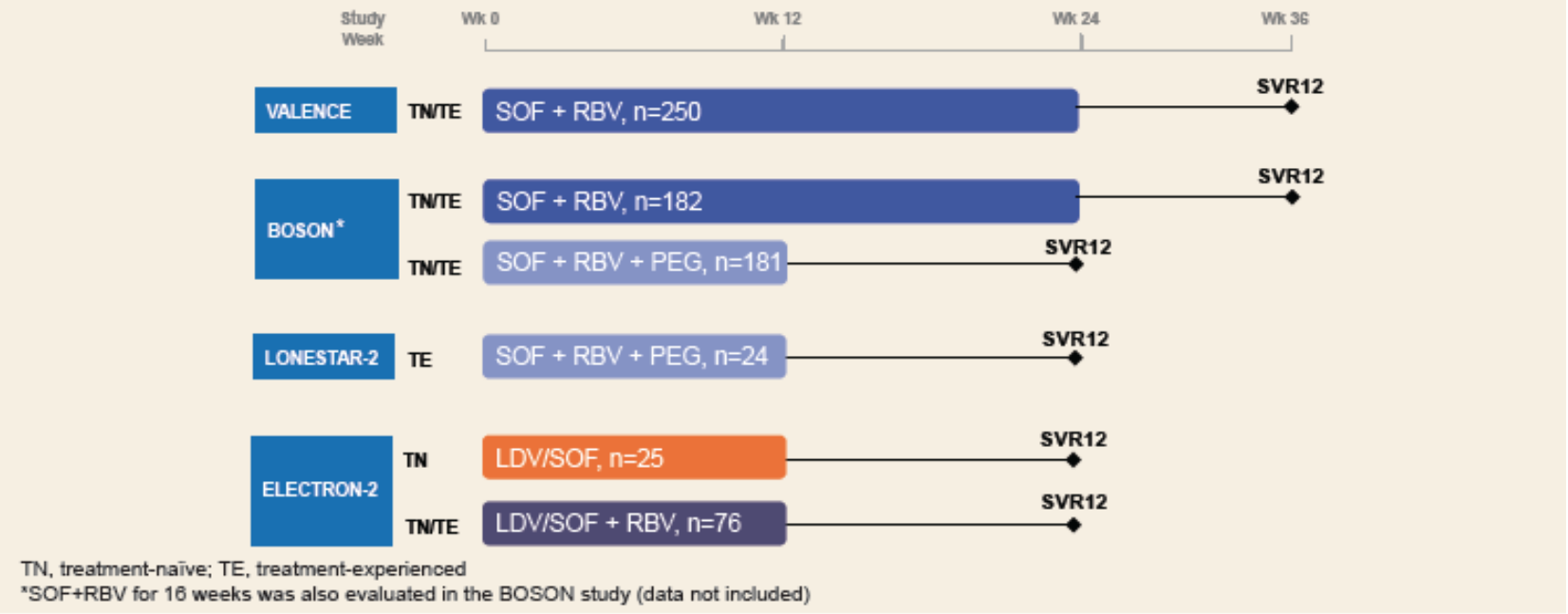
Nelson D, et al. *J Hepatol.* 2015;62(suppl 2):S624. Abstract P0782.

All-oral 12-week combination treatment with daclatasvir and sofosbuvir in treatment-experienced patients infected with HCV genotype 3: a sub-analysis of the ALLY-3 phase 3 study. (Nelson et al. Abstract P0782)

- No virologic breakthroughs
- Virologic relapse (n=7 with analyzable sequences)
  - Cirrhosis (n=4)
  - Treatment-emergent Y93H (n=4) and L31I (n=1)
- Generally safe and well tolerated
  - No deaths, treatment-related serious adverse events, or discontinuations due adverse events
  - Most common adverse events: headache, fatigue, nausea
- Further options for optimizing SVR rates with daclatasvir + sofosbuvir in genotype 3 patients with cirrhosis are being evaluated (ALLY-3+ study: DCV/SOF+RBV for 12w vs. 16w)

Nelson D, et al. *J Hepatol.* 2015;62(suppl 2):S624. Abstract P0782.

Sofosbuvir-Based Regimens for Patients With HCV Genotype 3: Summary Results From the VALENCE, LONESTAR-2, and ELECTRON-2 Studies (Lawitz et al. Abstract Tu1018)

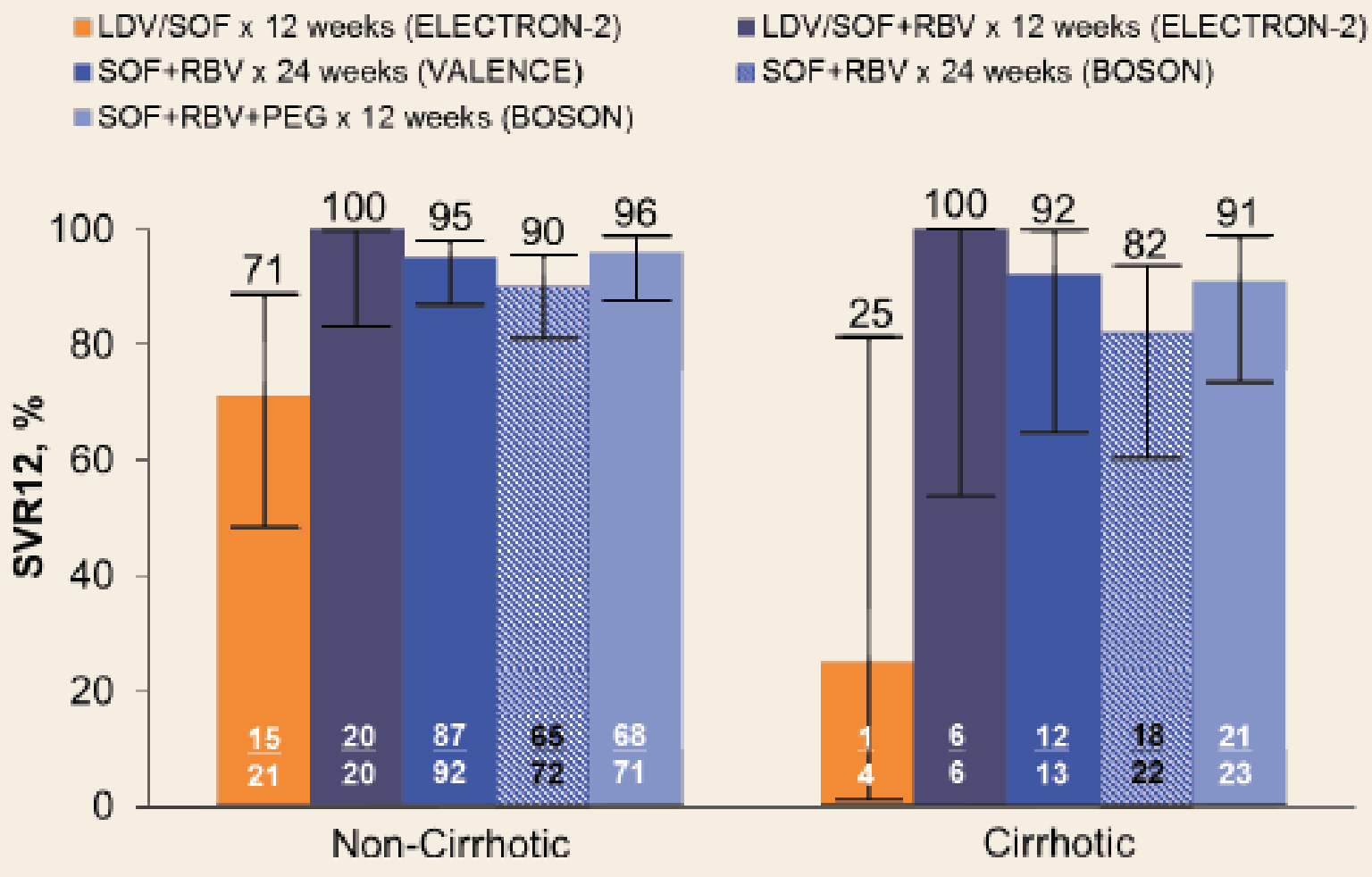


TN, treatment-naïve; TE, treatment-experienced
*SOF+RBV for 16 weeks was also evaluated in the BOSON study (data not included)

- Inclusion criteria had no upper limit to age or body mass index
- Minimum platelet count at screening
  - VALENCE[3]: ≥50,000 cells/mL
  - BOSON[4]: ≥60,000 cells/mL
  - LONESTAR-2[5]: ≥90,000 cells/mL (or ≥ 75,000/µL for patients with cirrhosis)
  - ELECTRON-2[6,7]: ≥50,000 cells/mL
- Primary efficacy endpoint - HCV RNA <LLOQ at post-treatment Week 12
  - VALENCE, LONESTAR-2, ELECTRON-2: analyzed by COBAS® TaqMan® HCV Test v2.0 HPS (LLOQ of <25 IU/mL)
  - BOSON: analyzed by Ampliprep TaqMan® HCV Test v2.0 (LLOQ <15 IU/mL)
- Primary safety endpoints - adverse events, discontinuations, and laboratory abnormalities

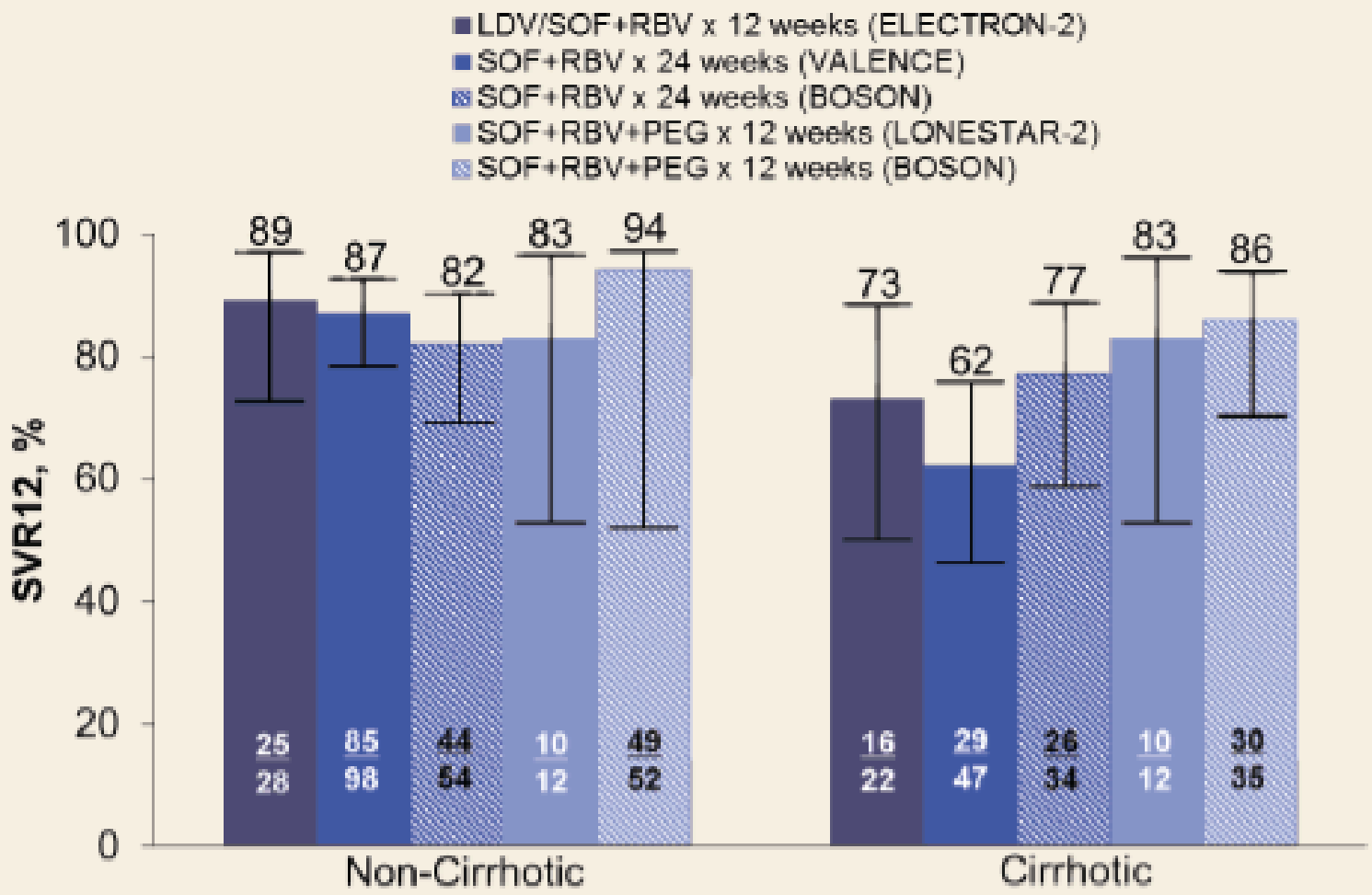
Sofosbuvir-Based Regimens for Patients With HCV Genotype 3: Summary Results From the VALENCE, LONESTAR-2, and ELECTRON-2 Studies (Lawitz et al. Abstract Tu1018)

SVR12 Among Treatment-Naïve Subjects

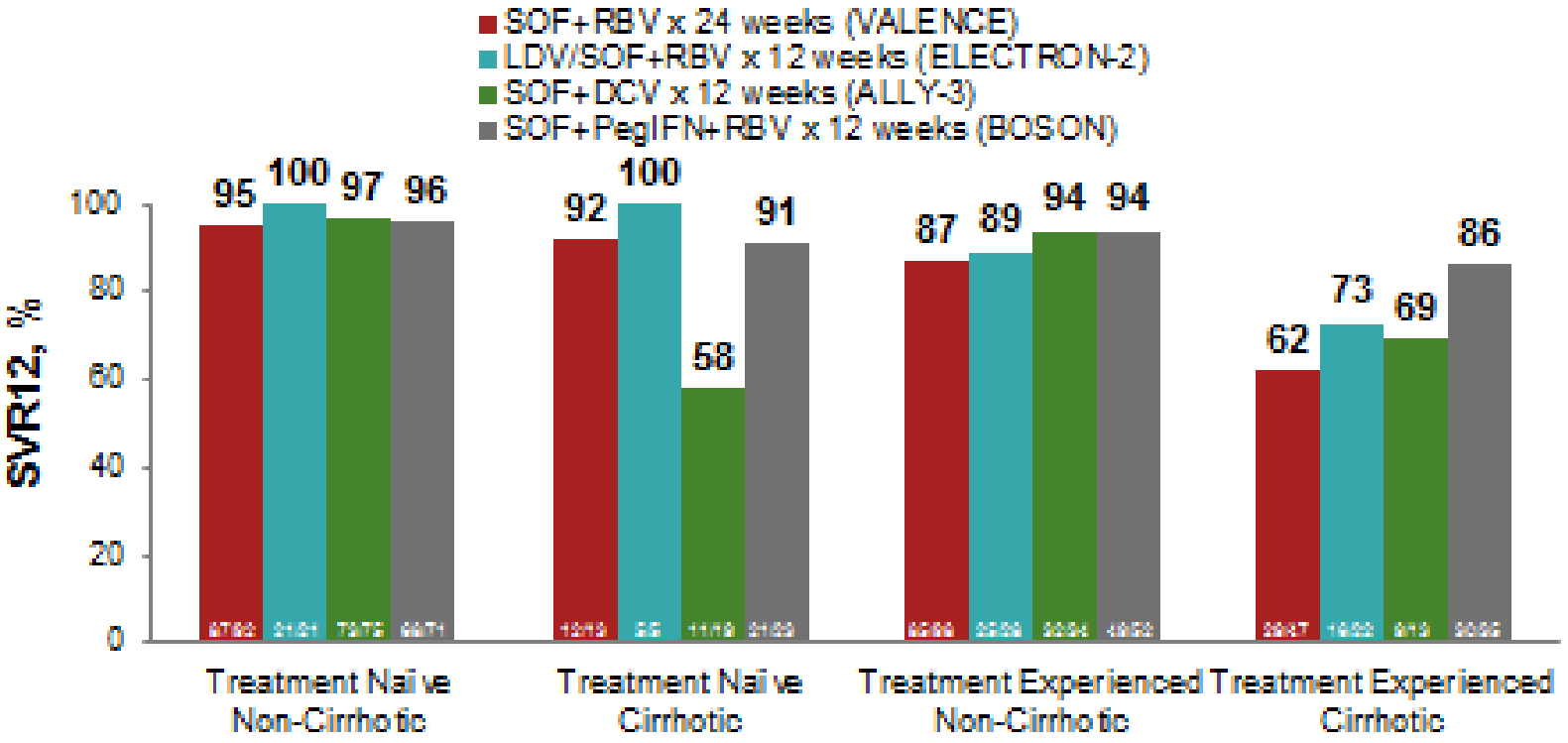


Sofosbuvir-Based Regimens for Patients With HCV Genotype 3: Summary Results From the VALENCE, LONESTAR-2, and ELECTRON-2 Studies (Lawitz et al. Abstract Tu1018)

SVR12 Among Treatment-Experienced Subjects



SOF-Based Regimens for HCV GT 3



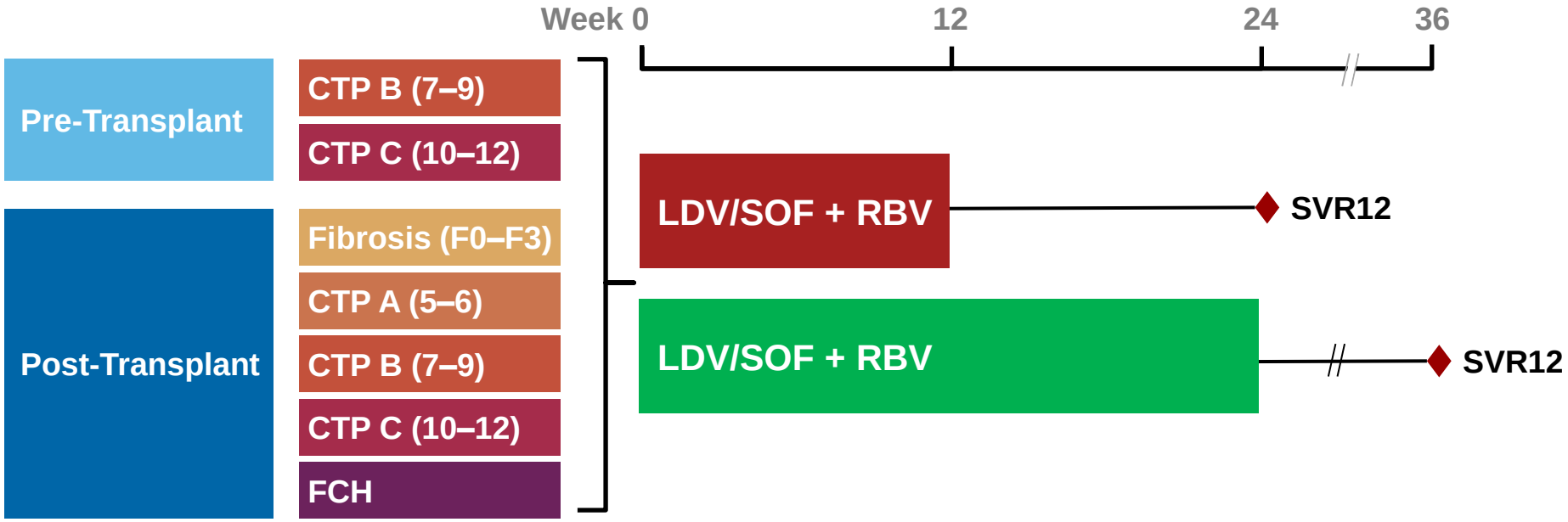
SOF-based regimens resulted in similar SVR12 rates in TN and TE HCV GT 3

Zeuzem S, et al. NEJM. 2014.
Gane, EJGL., 2014, Oral #8
Gane, AASLD, 2014, Poster #LB-11
Foster, EJGL., 2015, Oral #LO2
Nelson, D., et al. Hepatology 2015;61:1127-1135

HCV – Decompensated and Post-LT

- Any further data to help guide us in these tough patient populations?

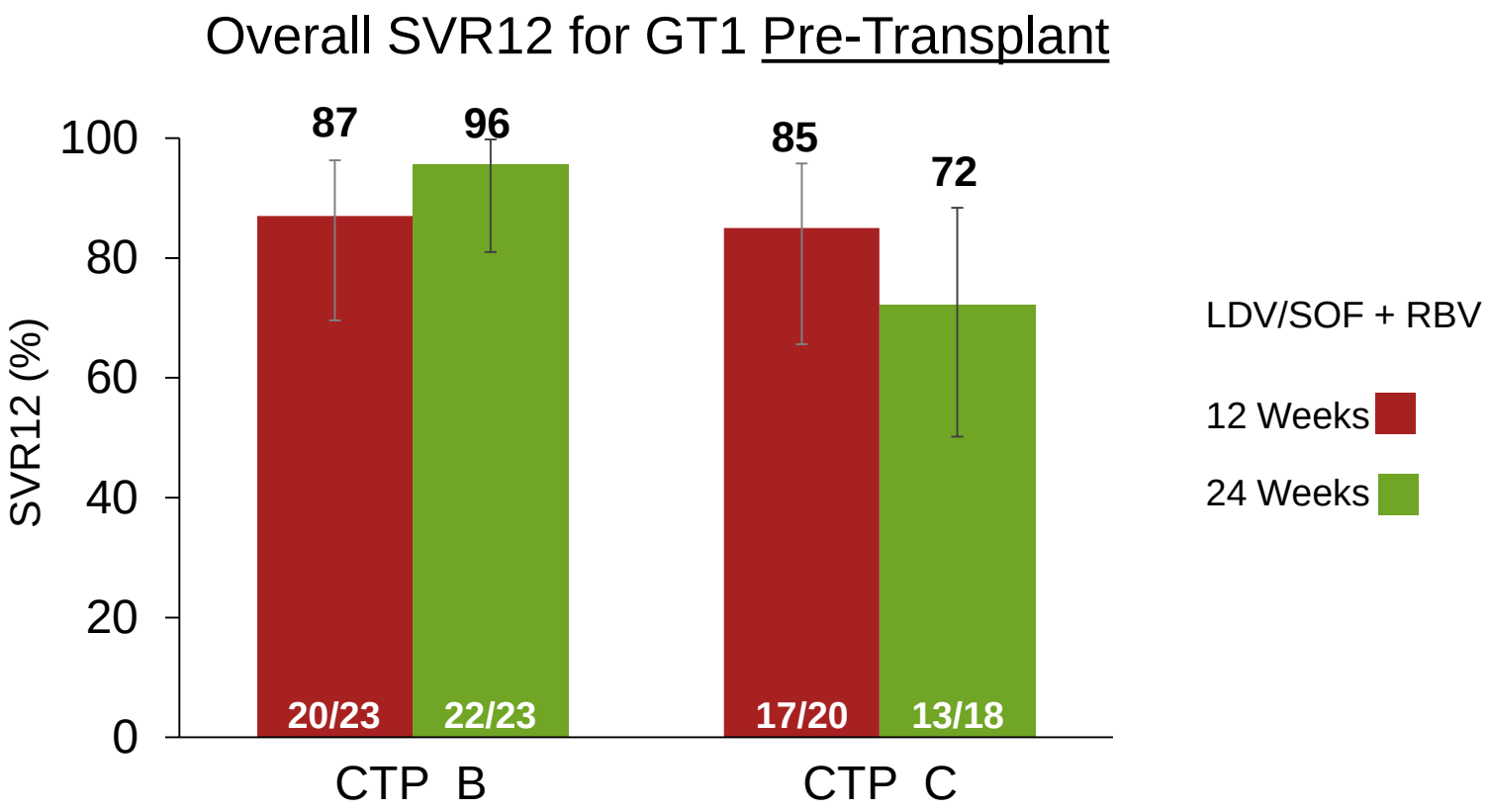
Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Prelim Results of the SOLAR-2 Study (M. Manns et al, Abstract G02)



- Inclusion criteria:
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤ 10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl ≥ 40 mL/min, Platelets > 30,000/mL
- RBV dosing
  - F0–F3 and CTP A cirrhosis: weight-based (< 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
  - CTP B and C cirrhosis: dose escalation: start at 600mg/d, titrate to max 1200 mg/d

Manns, EASL, 2015, GO2

Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Prelim Results of the SOLAR-2 Study (M. Manns et al, Abstract G02)

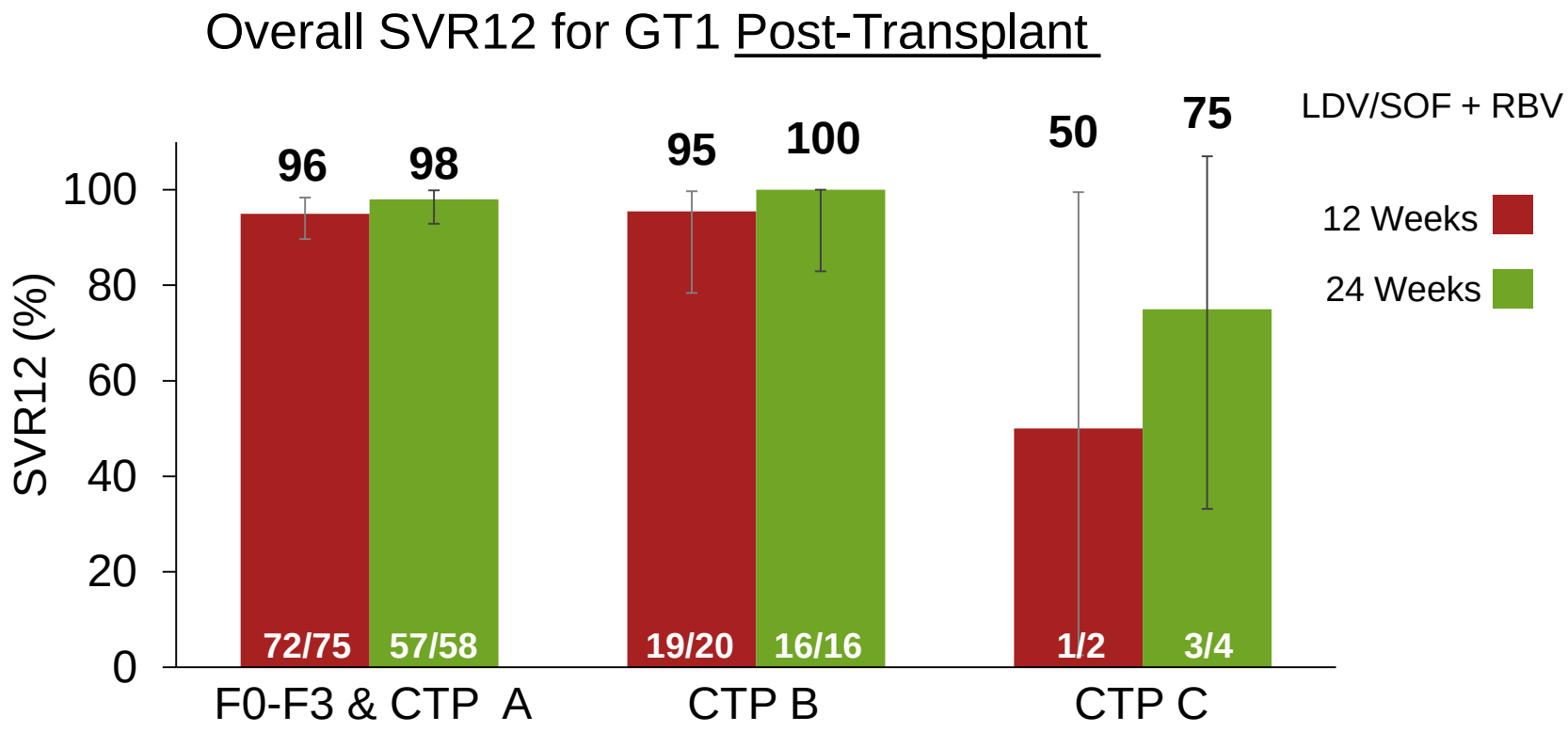


SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

27 subjects in the 24 week arm have not reached SVR12
7 subjects who were transplanted and 3 subjects did not meet inclusion criteria are excluded.
Error bars represent 2-sided exact 90% confidence intervals.

Manns, EASL, 2015, GO2

Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Prelim Results of the SOLAR-2 Study (M. Manns et al, Abstract G02)



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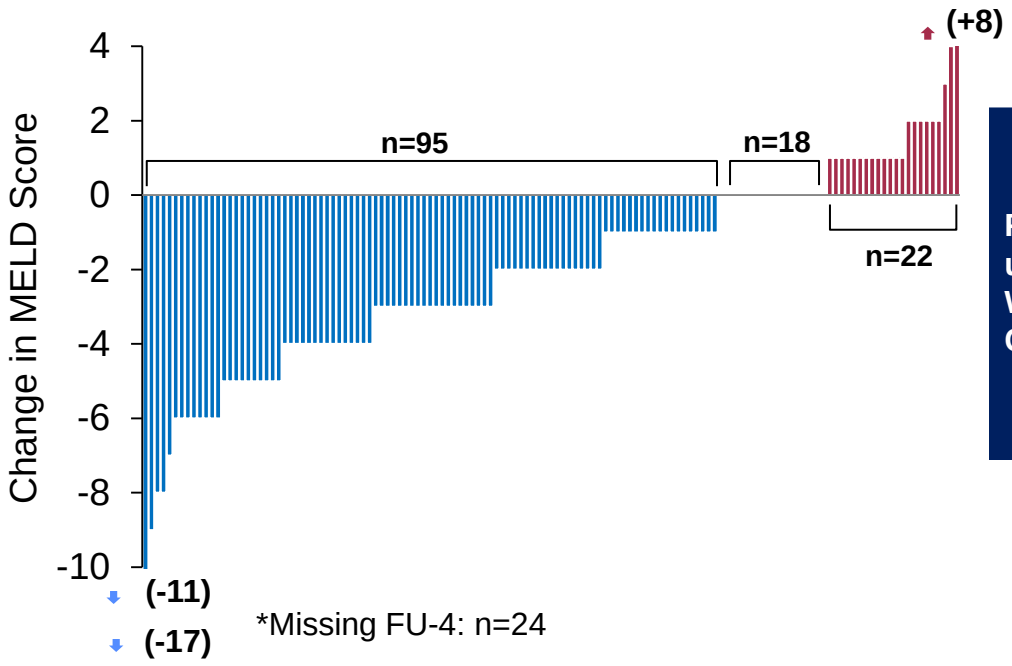
MELD Score Change

Pre/Post-Transplant (CTP B and C, n=136*)



*Missing FU-4: n=24

Change in CTP Class

		Baseline CTP		
		A (5–6) n=73	B (7–9) n=100	C (10–12) n=54
Follow-up Week 4 CTP	A (5–6)	67 (96)	31 (35)	2 (5)
	B (7–9)	3 (4)	57 (65)	20 (48)
	C (10–12)	0	0	20 (48)

no assessment: CTP A, n=3; CTP B, n=12; CTP C, n=12

Majority of patients showed improvements in MELD and CTP scores

Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Prelim Results of the SOLAR-2 Study (M. Manns et al, Abstract G02)

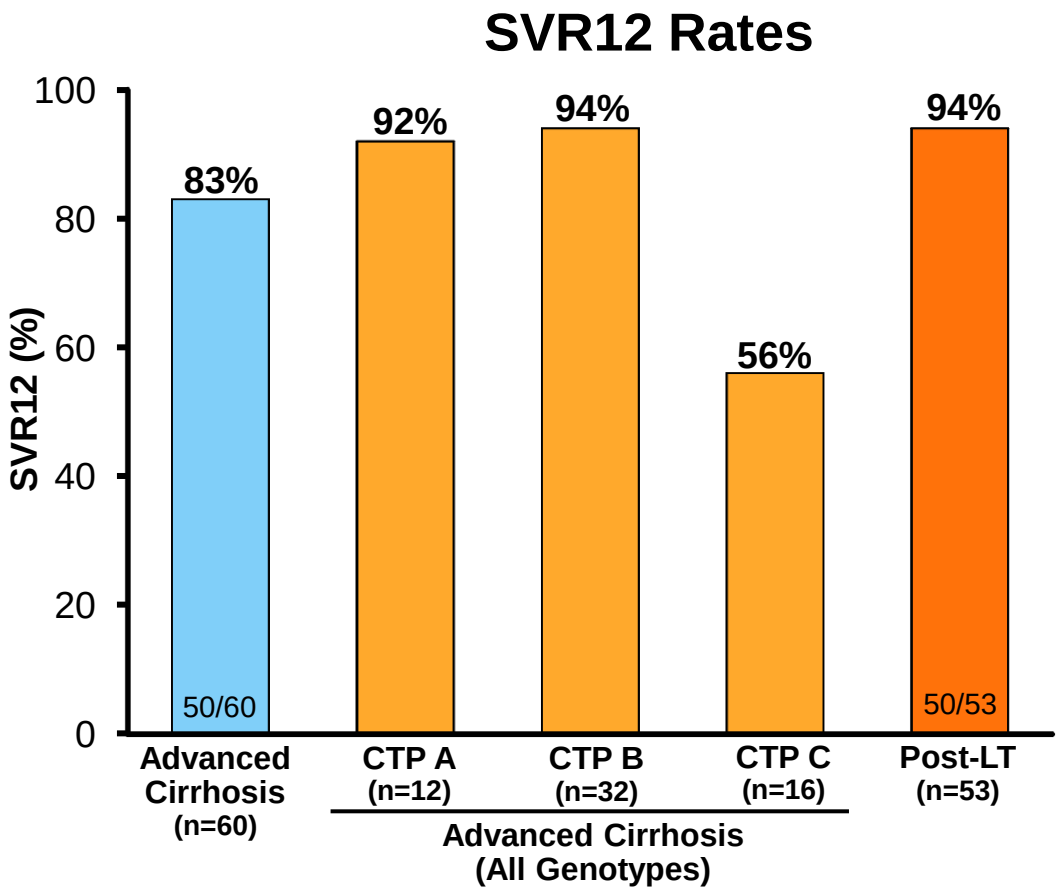
		Post-Transplant		Pre/Post-Transplant	
		F0–F3 + CTP A		CTP B + CTP C	
	Patients, n (%)	**12 Weeks n=86**	**24 Weeks n=82**	**12 Weeks n=78**	**24 Weeks n=82**
Overall Safety	AE	79 (92)	78 (95)	74 (95)	77 (94)
	Grade 3–4 AE	16 (19)	20 (24)	15 (19)	25 (30)
	SAE	12 (14)	12 (15)	22 (28)	23 (28)
	Treatment-related SAEs*	0	3 (4)	2 (3)	4 (5)
	Treatment D/C due to AE†	0	1 (1)	1 (1)	4 (5)
	Death	2 (2)	1 (1)	3 (4)	4 (5)

*Fall, anemia (5), vomiting, diarrhea, hyperbilirubinemia; †edema, dehydration, HCC (2), type 2 diabetes mellitus, hyperbilirubinemia.

- Regimen was safe and well tolerated with low D/C due to AE
- No deaths were considered treatment related

Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: phase 3 ALLY-1 study. (Poordad et al. Abstract L08)

- Phase 3 study
  - Genotype 1, 2, 3, 4, or 6
  - Treatment-naïve or experienced
  - Advanced cirrhosis (n=60)
  - Post-transplant (n=53)
- Daclatasvir 60 mg + sofosbuvir 400 mg + RBV 600->1000mg for 12 weeks
- No events of graft rejection
- Relapses (all had NS5A RAVs at relapse)
  - Advanced cirrhosis (n=10)
  - Posttransplant (n=3)
- Majority of treatment discontinuations were RBV-related



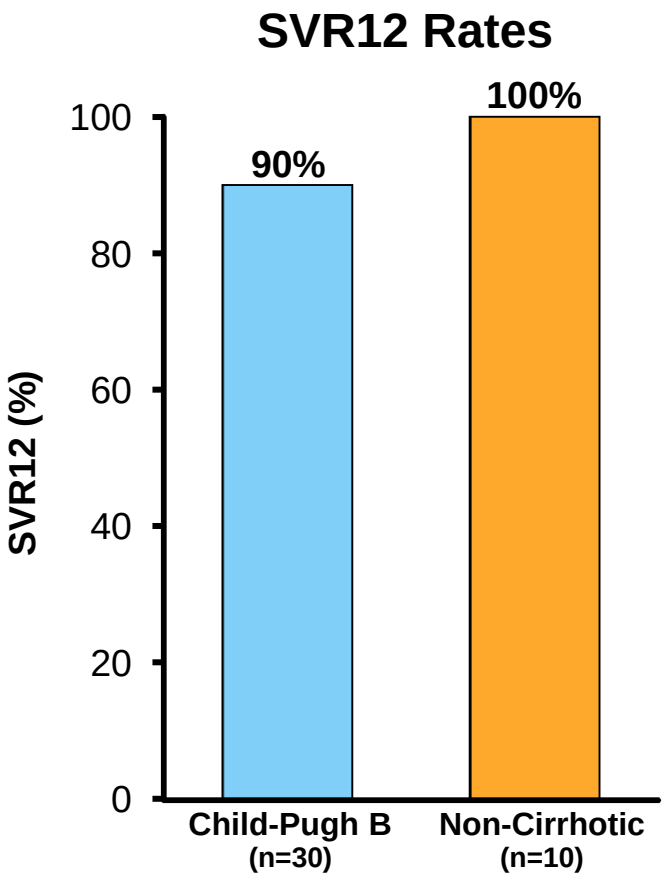
CTP: Child-Tucotte-Pugh class.
RBV 600 mg, adjusted based on hemoglobin levels and creatinine clearance.
Advanced cirrhosis: MELD 8-40; HCC allowed.
Post-liver transplantation: >3 months posttransplant; no evidence of rejection; any immunosuppressive regimen.

Poordad F, et al. *J Hepatol.* 2015;62(suppl 2):S261. Abstract L08.

GT3: 5/6 and 10/11 w/ SVR12

Efficacy and safety of grazoprevir and elbasvir In hepatitis C genotype 1-infected patients with Child–Pugh class B cirrhosis (C-SALT PART A). (Jacobson et al. Abstract O008)

- Phase 2, open-label study
  - Genotype 1
  - Child-Pugh B (n=30)
  - Non-cirrhotic (n=10)
- Grazoprevir/elbasvir ***50***/50 mg daily for CTP-B
- Grazoprevir/elbasvir ***100***/50 mg daily for non-cirrhotic PK controls
- Relapse (n=2, both with genotype 1a)
- Pharmacokinetics
  - Grazoprevir exposure: slightly higher in CTP-B
  - Elbasvir exposure: similar in both groups
- Safety
  - No discontinuations due to adverse events
  - One death related to SBP, liver failure
  - No treatment-related deaths or serious adverse events



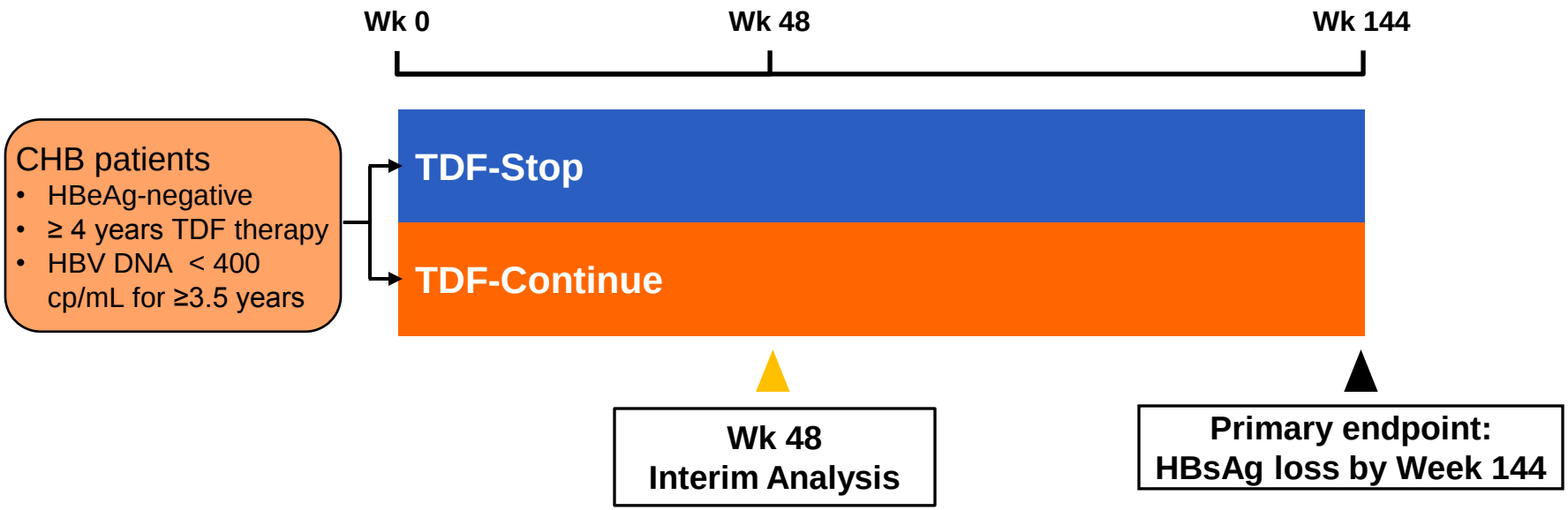
Jacobson IM, et al. *J Hepatol.* 2015;62(suppl 2):S193-S194. Abstract O008.

HBV

- Can we ever stop these oral antivirals?

Stopping Tenofovir After Long Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results (Finite CHB Trial). (Berg et al. Abstract O119)

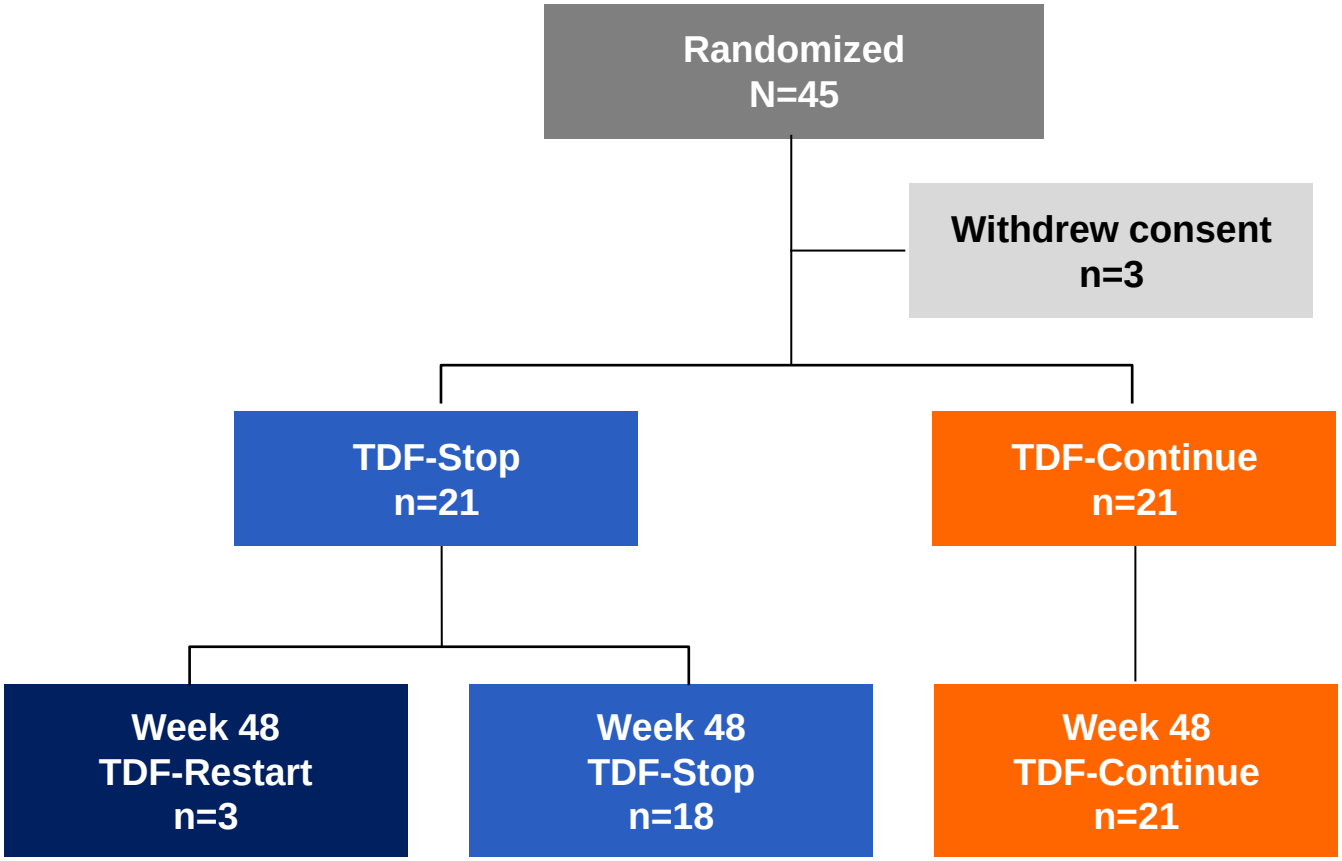
Open-label, multicenter, randomized, controlled trial, Week 48 interim analysis



- No cirrhosis (Fibroscan ≤10 kPa), normal ALT, HBeAg-, anti-HBe+, HBsAg+
- No history of decompensated liver disease
- "Stop and Relapse" approach to induce HBsAg loss
- TDF restart criteria based on viral load, ALT, prothrombin time, and bilirubin

Berg, EASL, 2015, O119

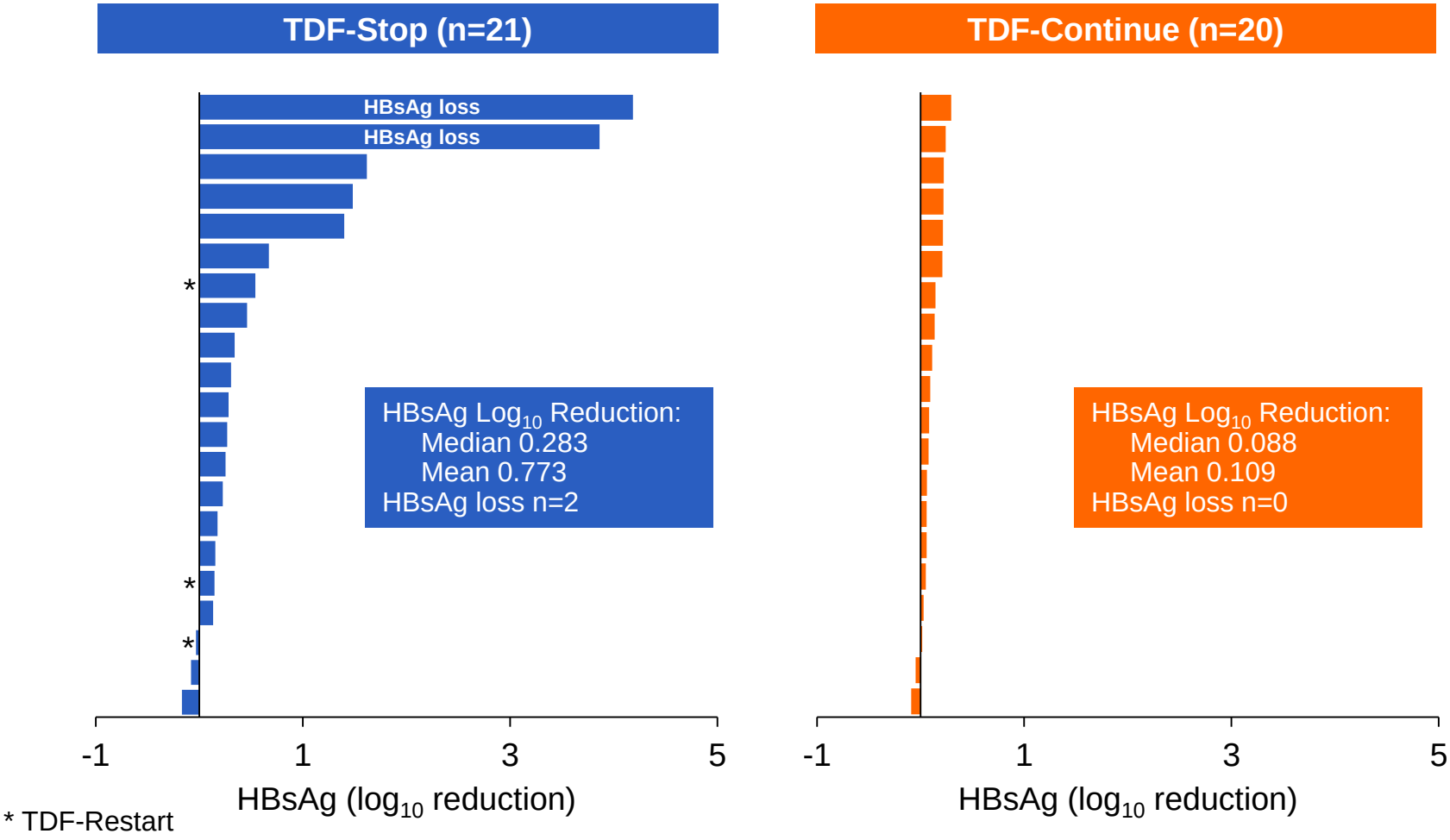
Stopping Tenofovir After Long Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results (Finite CHB Trial). (Berg et al. Abstract O119)



86% of TDF-Stop subjects did not restart TDF by Week 48

Berg, EASL, 2015, O119

Stopping Tenofovir After Long Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results (Finite CHB Trial). (Berg et al. Abstract O119)

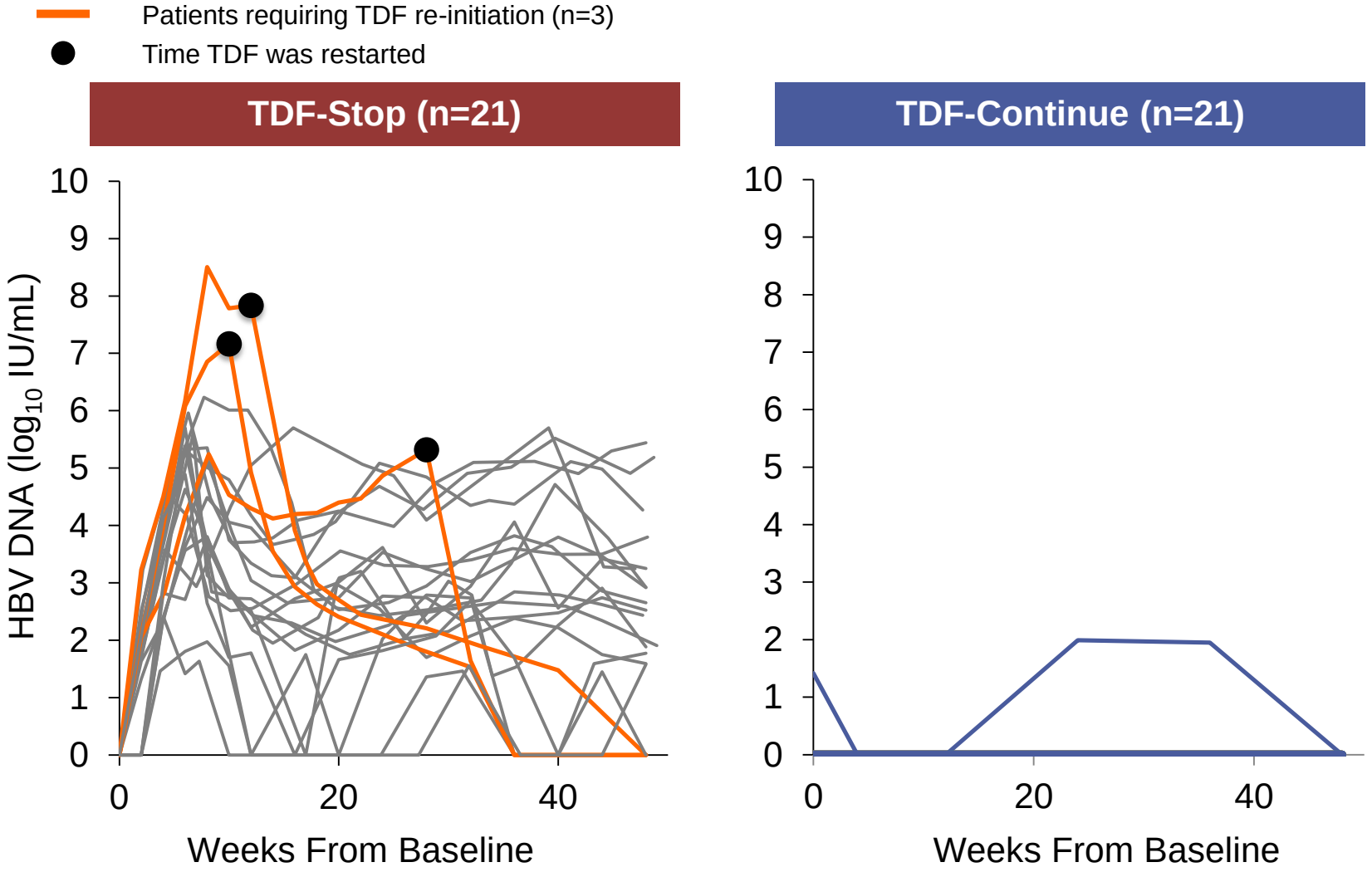


* TDF-Restart

Stopping TDF was associated with a more profound decline in HBsAg levels compared to continuous TDF

Berg, EASL, 2015, O119

Stopping Tenofovir After Long Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results (Finite CHB Trial). (Berg et al. Abstract O119)



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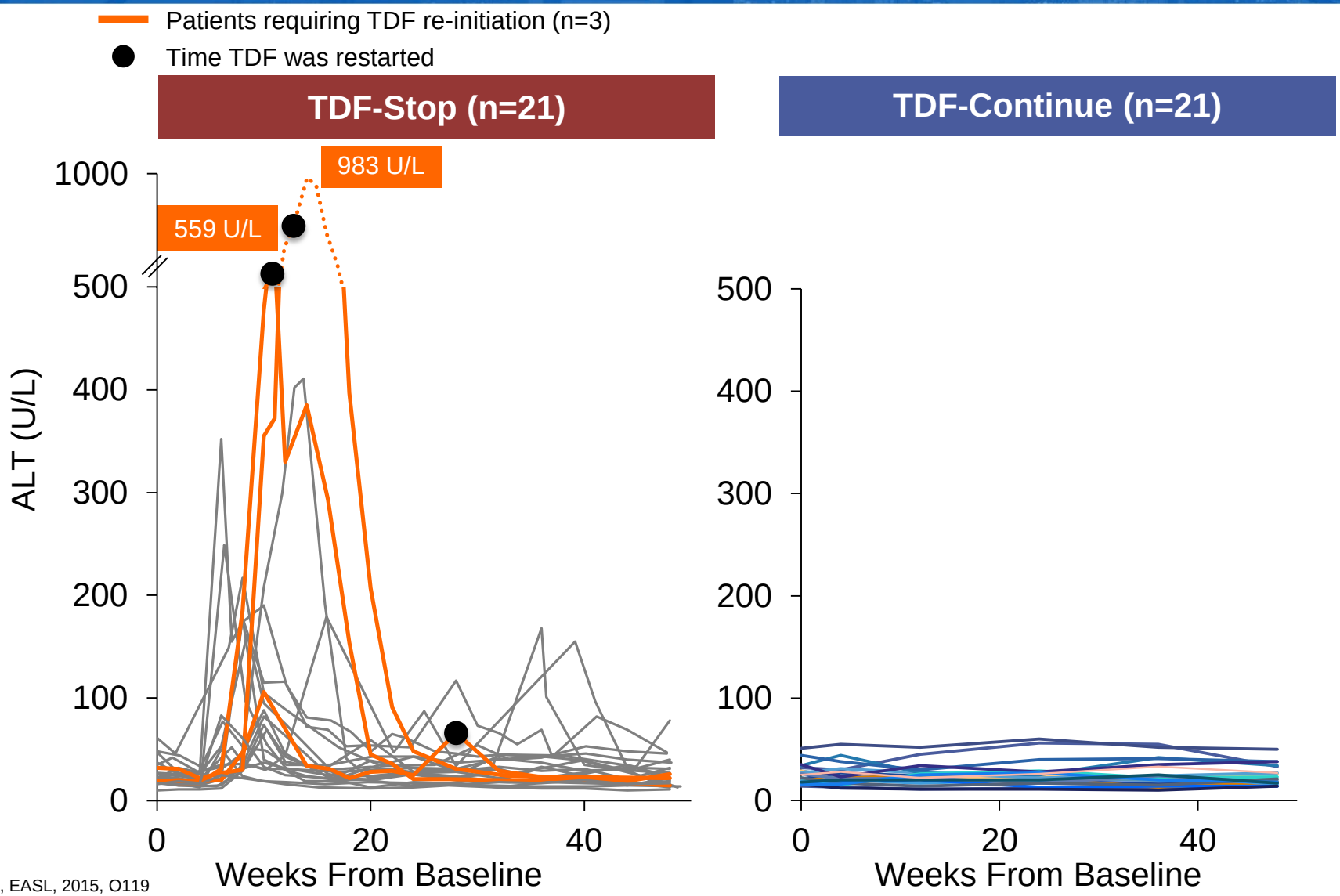

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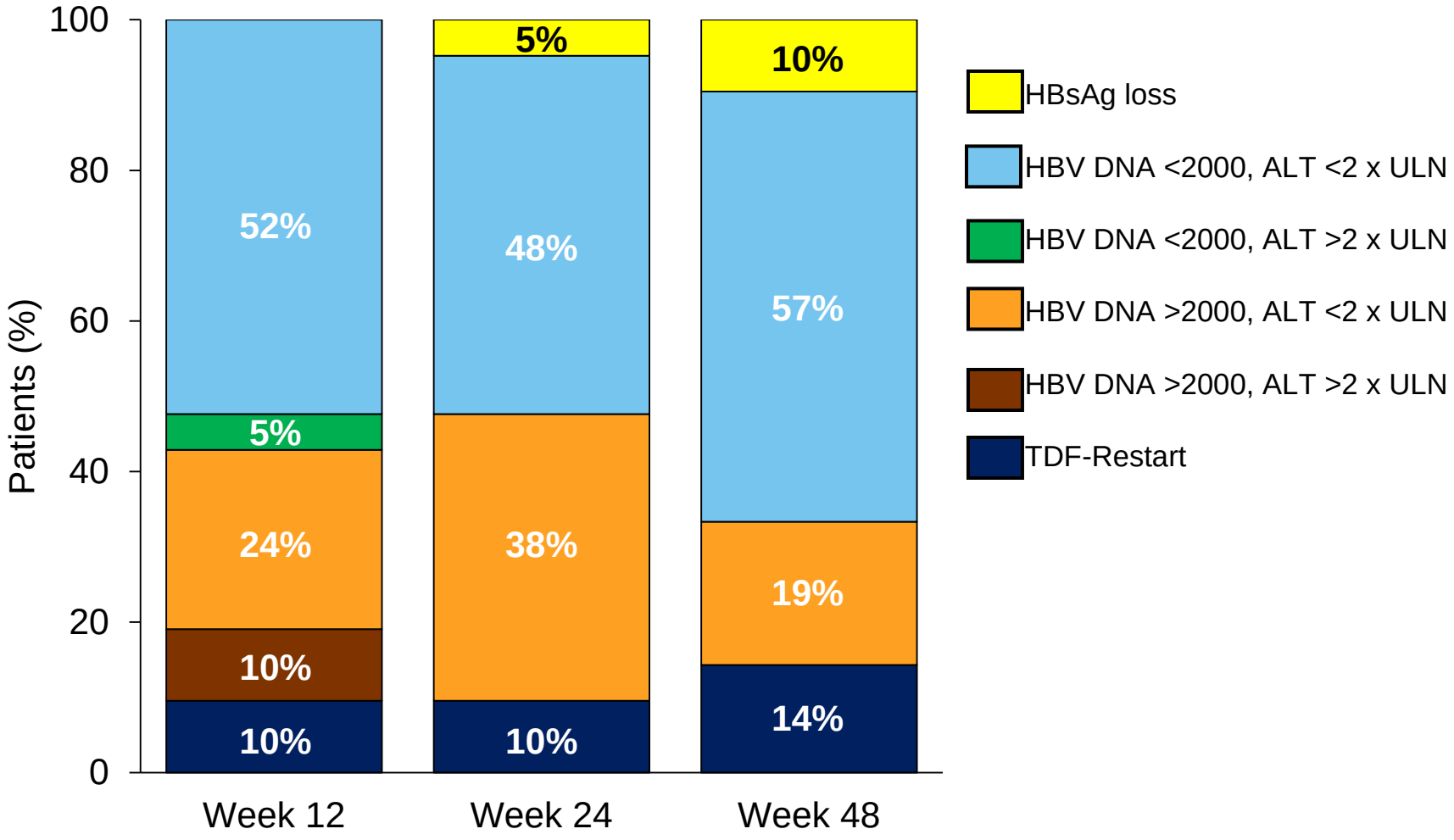


Berg, EASL, 2015, O119

Stopping Tenofovir After Long Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results (Finite CHB Trial). (Berg et al. Abstract O119)

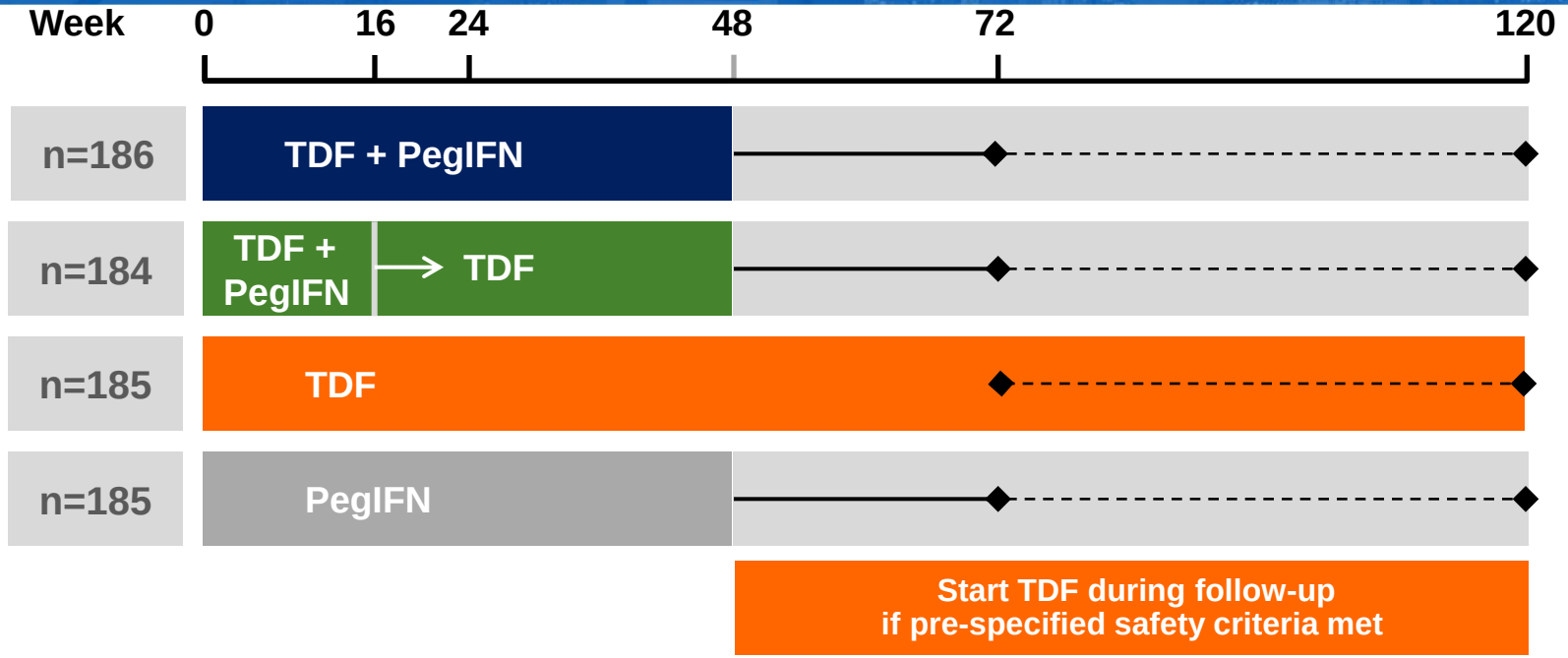
- Stopping TDF in HBeAg-negative patients with undetectable HBV DNA for at least 3.5 years appears to be safe
  - No cirrhotic patients at baseline
- 86% of TDF-Stop subjects did not restart TDF by Week 48
- Stopping TDF was associated with a more profound decline in HBsAg levels compared to continuous TDF (0.283 vs 0.088 log reduction, respectively)
  - HBsAg loss was observed in two subjects (9.5%) 48 weeks after TDF discontinuation
- These data support the concept of stopping antiviral therapy in long-term HBV DNA-suppressed subjects without cirrhosis

Berg, EASL, 2015, O119

HBV - Interferon

- Is interferon for HBV making a comeback?

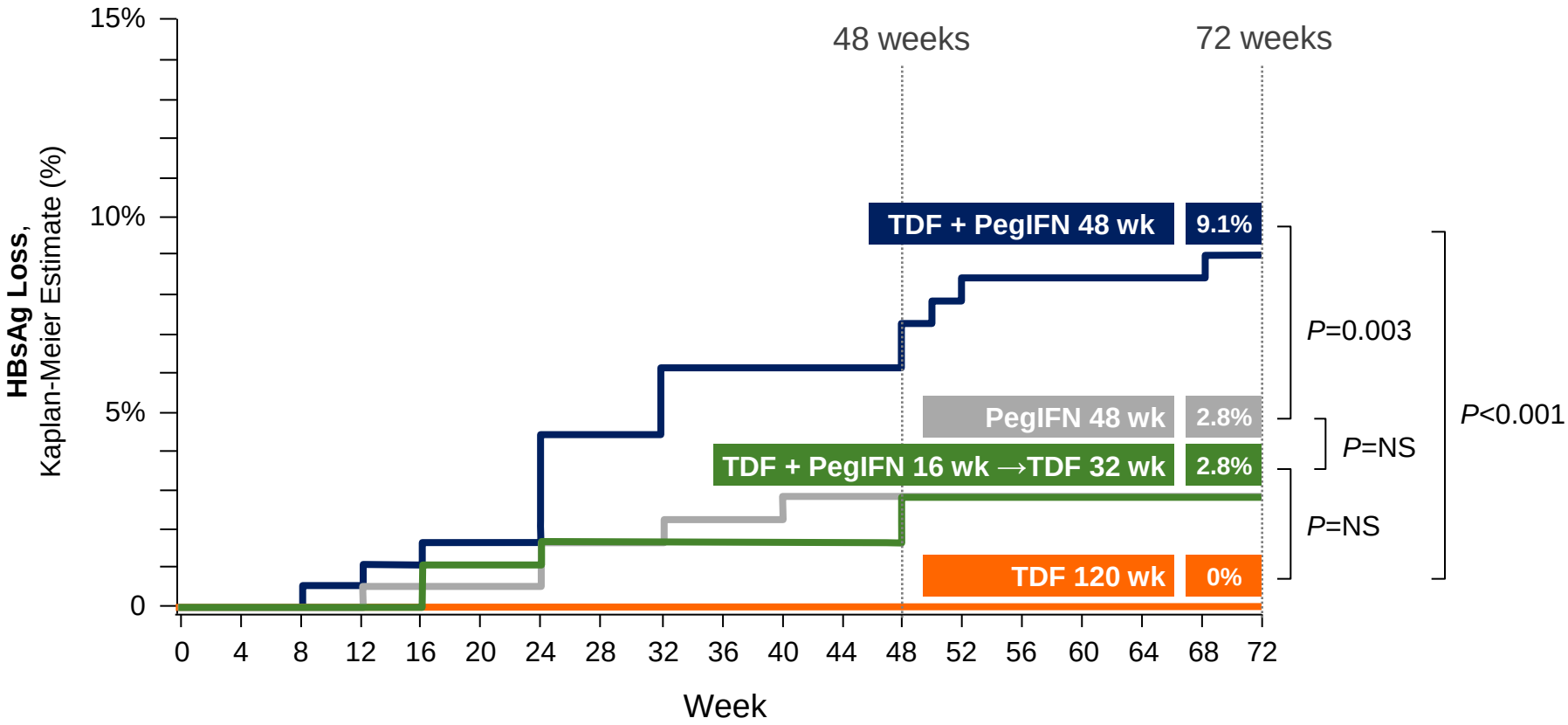
Predictors of Clinical Response: Results from a large RCT with TDF + PegIFN-2a for CHB. (Chan et al. Abstract O117)



- Randomized, controlled, open-label study (N=740)
  - Stratified by HBeAg status and HBV genotype
- Primary endpoint: HBsAg loss at Week 72 by Kaplan-Meier estimate
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥ 20,000 IU/mL; HBeAg- and HBV DNA ≥ 2,000 IU/mL
  - ALT > 54 and ≤ 400 U/L (men); ALT > 36 and ≤ 300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Chan, EASL, 2015, O117
Marcellin, APASL, 2015, Oral #1993
Marcellin, AASLD, 2014, Oral #193

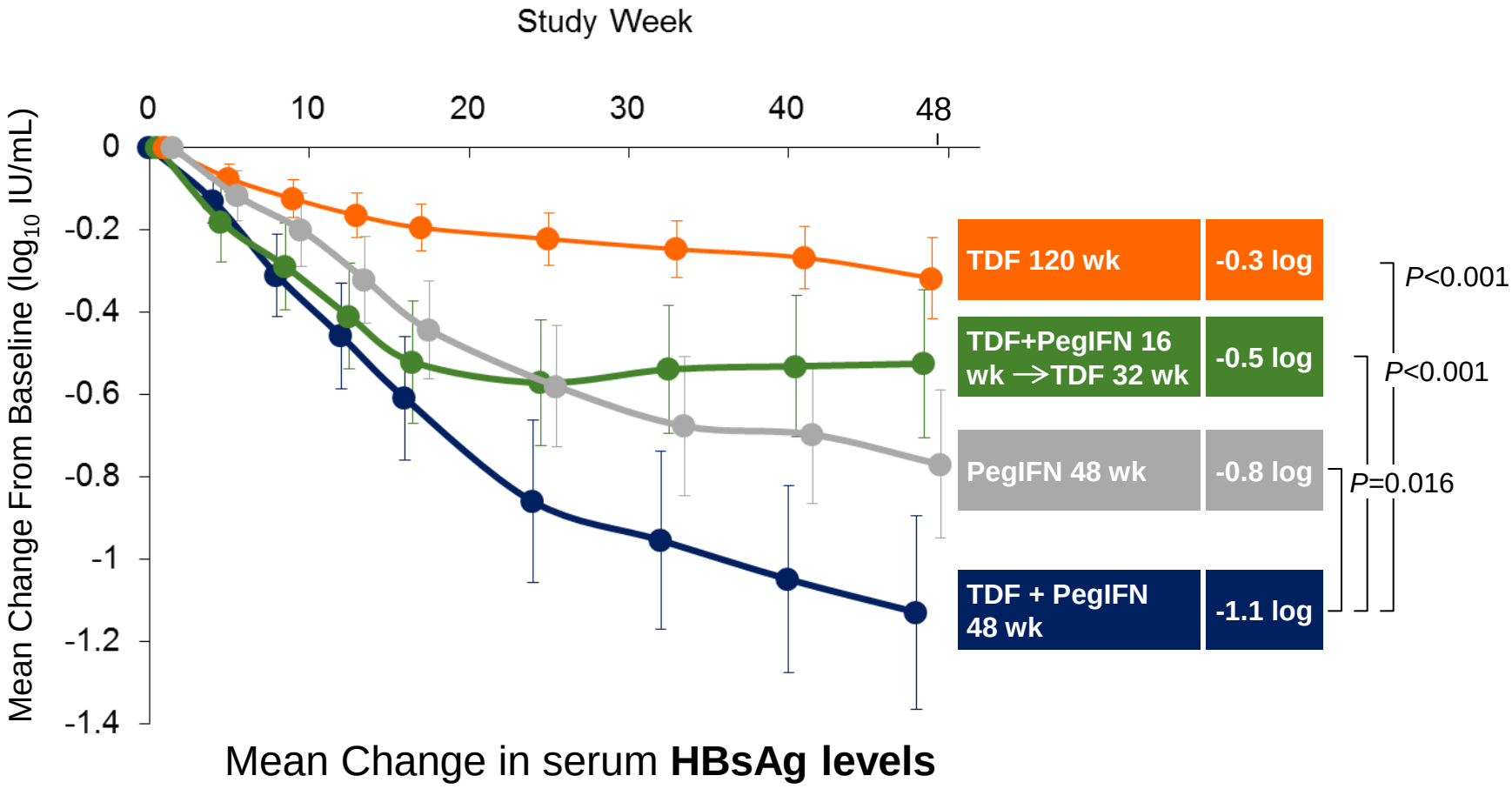
Predictors of Clinical Response: Results from a large RCT with TDF + PegIFN-2a for CHB. (Chan et al. Abstract O117)



- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PegIFN 48 wk], 3 [TDF + PegIFN 16 wk →TDF 32 wk])
  - 5/7 had ≤ 1 week of therapy after HBsAg loss

Chan, EASL, 2015, O117
Marcellin, APASL, 2015, Oral #1993
Marcellin, AASLD, 2014, Oral #193

Predictors of Clinical Response: Results from a large RCT with TDF + PegIFN-2a for CHB. (Chan et al. Abstract O117)



Error bars represent 95% confidence intervals

Chan, EASL, 2015, O117
Marcellin, APASL, 2015, Oral #1993
Marcellin, AASLD, 2014, Oral #193

Predictors of Clinical Response: Results from a large RCT with TDF + PegIFN-2a for CHB. (Chan et al. Abstract O117)

TDF + PegIFN 48 wk

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
HBsAg decline from baseline > 1 $\log_{10}$ at Week 12	71%	92%	43%	97%

- High negative predictive values are seen among patients treated with TDF + PegIFN combination if they have:
  - HBsAg decline < 1 $\log_{10}$ IU/mL at Week 12

Chan, EASL, 2015, O117

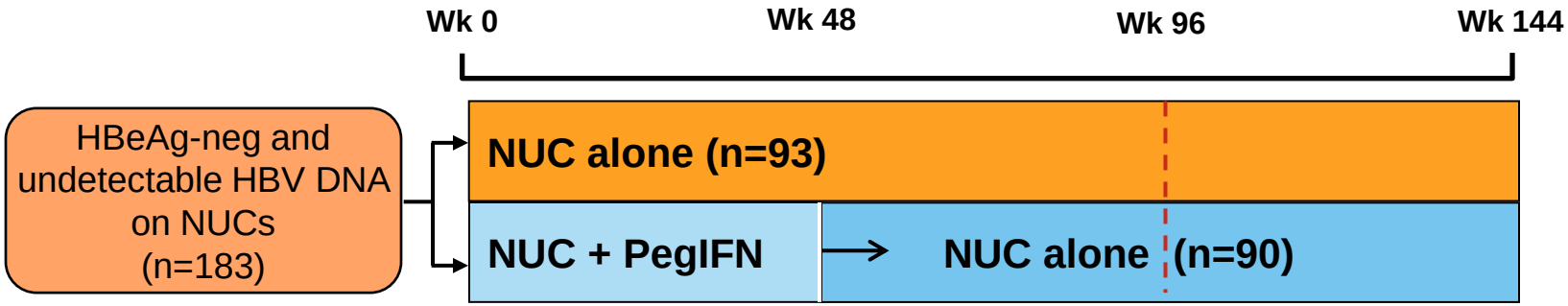
Predictors of Clinical Response: Results from a large RCT with TDF + PegIFN-2a for CHB. (Chan et al. Abstract O117)

- HBeAg status, TDF-containing treatment, baseline HBsAg and HBV DNA impact virologic response
  - HBV genotype A shows the largest HBsAg decline
  - HBV genotype D shows the lowest HBsAg decline
- TDF + PegIFN for 48 weeks induces more HBsAg decline and higher HBsAg loss than all other regimens tested in this study
- High negative predictive value for HBsAg loss among patients treated with TDF + PegIFN combination if they have:
  - HBsAg decline <1 $\log_{10}$ IU/mL at Week 12
- Future research to identify patient subpopulations who may derive the most benefit from combination therapy is warranted

Chan, EASL, 2015, O117
Marcellin, APASL, 2015, Oral #1993
Marcellin, AASLD, 2014, Oral #193

HBsAg Clearance After Addition of PegIFN for 48 Weeks in HBeAg-Negative CHB Patients on Nucleos(t)ide Therapy with Undetectable HBV DNA for at least one year: Final Results from PEGAN Study. Bourliere et al. Abstract O112)

Phase III Multicenter, randomized, controlled study in 183 patients.
Documented undetectable HBV DNA while on medications for at least 1 year



	NUCs Alone N=93	PegIFN + NUCs N=90	*P*-value
HBsAg loss (Week 48, %)	0 (0)	7 (8)	0.0057
HBsAg loss (Week 96, %) *(1° endpoint)*	3 (3)	7 (8)	0.1521
HBs seroconversion (Week 96, %)	1 (1)	6 (7)	0.0465

Patients receiving add-on PegIFN experienced higher HBsAg loss than NUC monotherapy at W48, but without statistical difference at W96

Bourliere, EASL, 2015, O112

Take Home

- SVR12 appears to be durable
- NS5A resistance:
  - often present at baseline
  - more prominent after relapse
  - may be clinically significant
- “Sim+Sof” – caution w/ shortened regimen
- Exciting drugs in the pipeline:
  - Daclatasvir (pangenotypic NS5A)
  - Grazoprevir/Elbasvir (pangenotypic NS3A/NS5A)
  - GS-9857, GS-5816 (pangenotypic NS3A/NS5A)
  - ACH-3102 (second generation NS5A)
- ESRD: (caution advised)
  - consider ombitasvir/paritaprevir/ritonavir plus dasabuvir
  - Sim+Sof or Sof+RBV
  - Grazoprevir/Elbasvir looks promising

Take Home - 2

- GT3:
  - For TN/TE Non-cirrhotic and TN Cirrhotic – either SOF+RBV 24w or LDV/SOF+RBV 12w
  - For TE Cirrhotic - SOF+ P/R for 12 weeks is still the best ☹
- Decompensated Cirrhosis – LDV/SOF + RBV for 12 weeks
- Post-LT – LDV/SOF + RBV for 12 weeks
- Relapse after LDV/SOF
  - Consider retreatment with LDV/SOF for 24 weeks (particularly if only Rx 8wk and/or no NS5A RAVs)
- HBV – suppressed on oral antivirals
  - consider stopping treatment (non-cirrhotic only)
  - consider adding pegylated IFN

Thank you!

- Questions?