LEDIPASVIR/SOFOSBUVIR en el entorno del Trasplante hepático

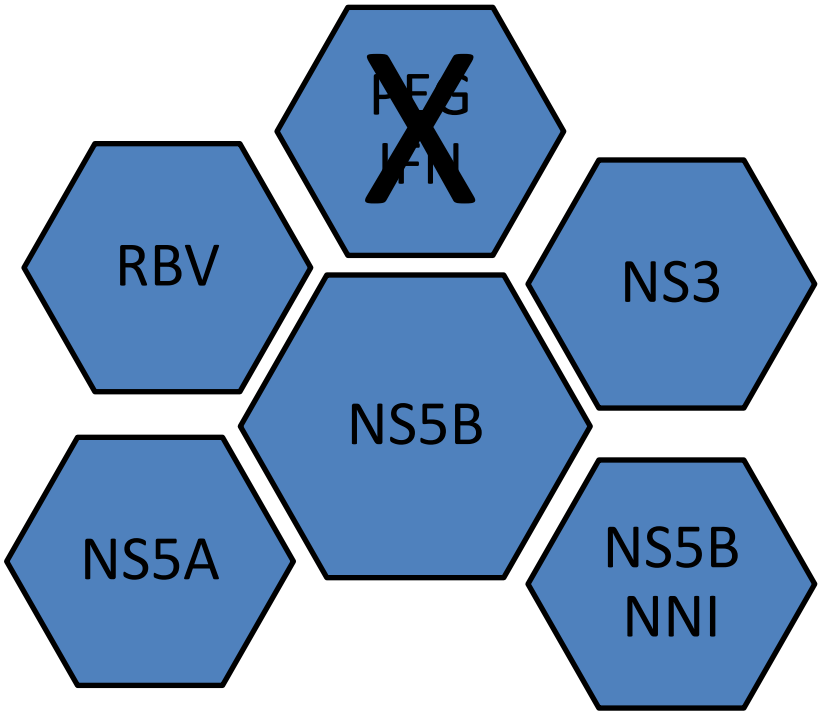
Martín Prieto Castillo
Unidad de Hepatología, Sº Medicina Digestiva
HUP La Fe, Valencia

HARVONI®
ledipasvir/sofosbuvir

Agenda

- Introducción. SOLAR 1-2
- LDV/SOF en Cirrosis descompensada
- LDV/SOF en Hepatitis C post-TH
- Recidiva virológica
- Seguridad LDV/SOF
- LDV/SOF en Guías EASL

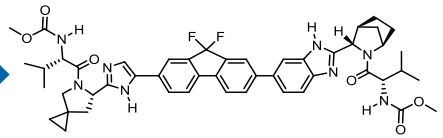
The Building Blocks for SVR in HCV pre or Post–Liver Transplantation



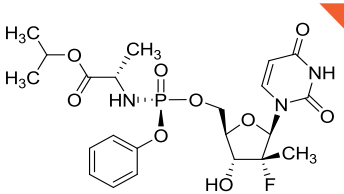
Ledipasvir/Sofosbuvir: A Single Tablet Regimen (STR)

- Ledipasvir
  - Picomolar potency against HCV GT 1a and 1b
  - Once-daily, oral, 90-mg

LDV NS5A inhibitor



- Sofosbuvir
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg



SOF nucleotide NS5B polymerase inhibitor

- Ledipasvir/Sofosbuvir FDC
  - Once-daily, oral, fixed-dose (90/400 mg) combination tablet
  - Single-tablet regimen (STR) for hepatitis C

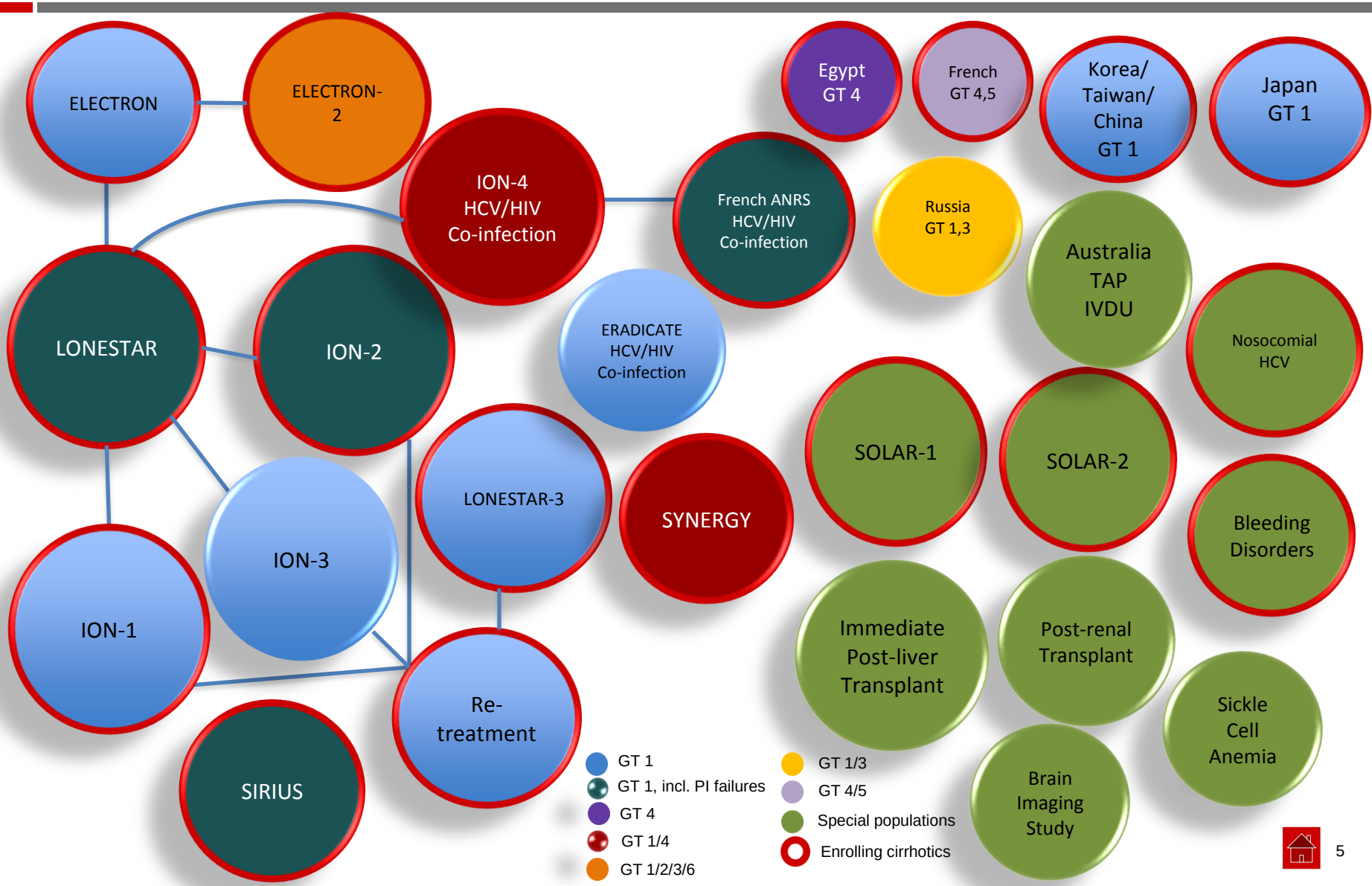
LDV NS5A inhibitor

SOF nucleotide NS5B polymerase inhibitor

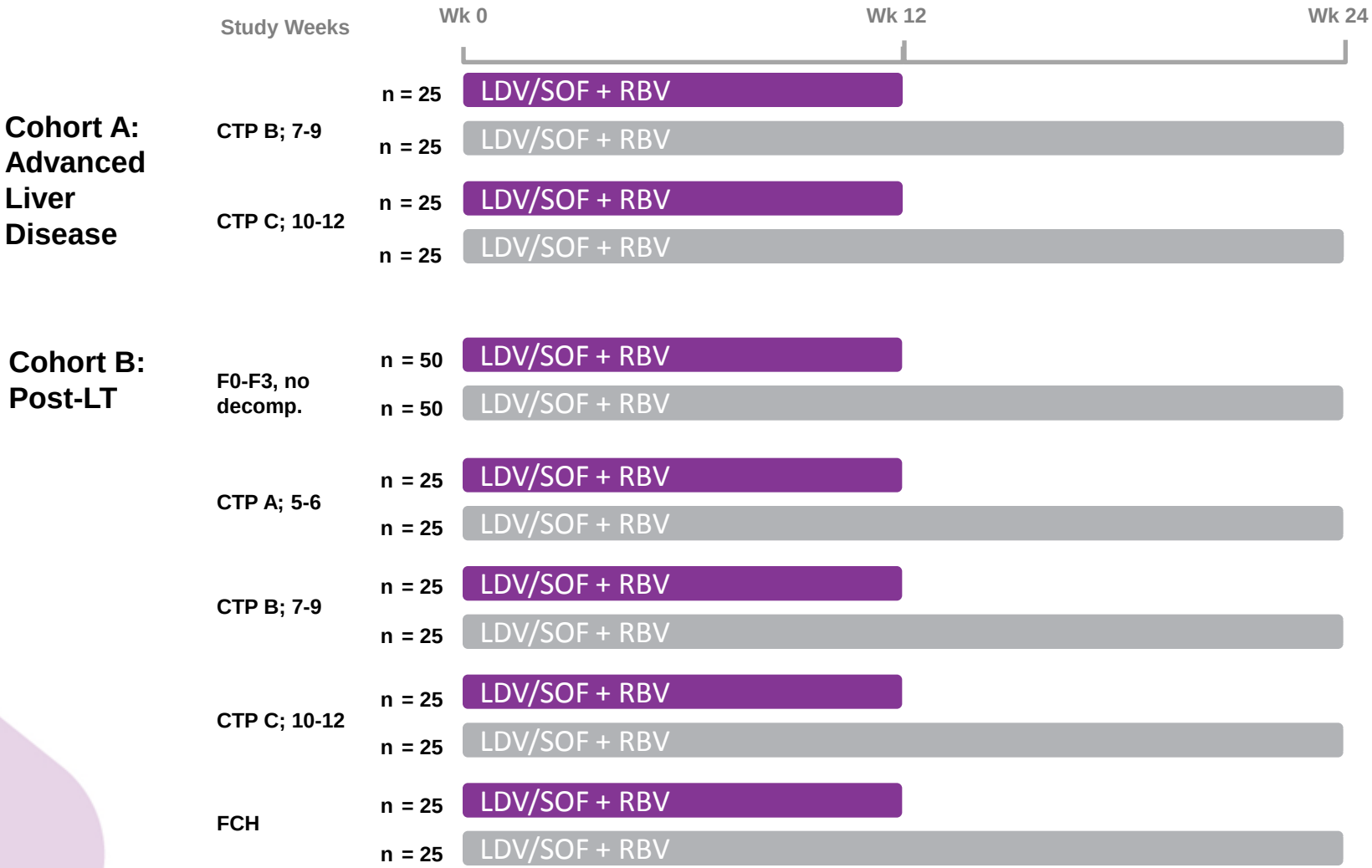
FDA Approval 10/10/14
Health Canada Approval 10/16/14
European Approval 11/18/14

FDC, fixed-dose combination

LDV/SOF Clinical Development Program



SOLAR-1/2: LDV/SOF + RBV for Treatment of HCV in Subjects with Decompensated Cirrhosis or Post-Transplant Recurrence



SOLAR-1 (US) Status: Groups 1-5 enrolled, interim CSR Jul 2014
SOLAR-2 (ex-US) Status: FSFV Jan 2014, enrolling

Clinicaltrials.gov NCT01938430

All arms continue with 5 years of long-term follow-up for clinical outcomes

HARVONI® ledipasvir/sofosbuvir

Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Decompensated Cirrhosis

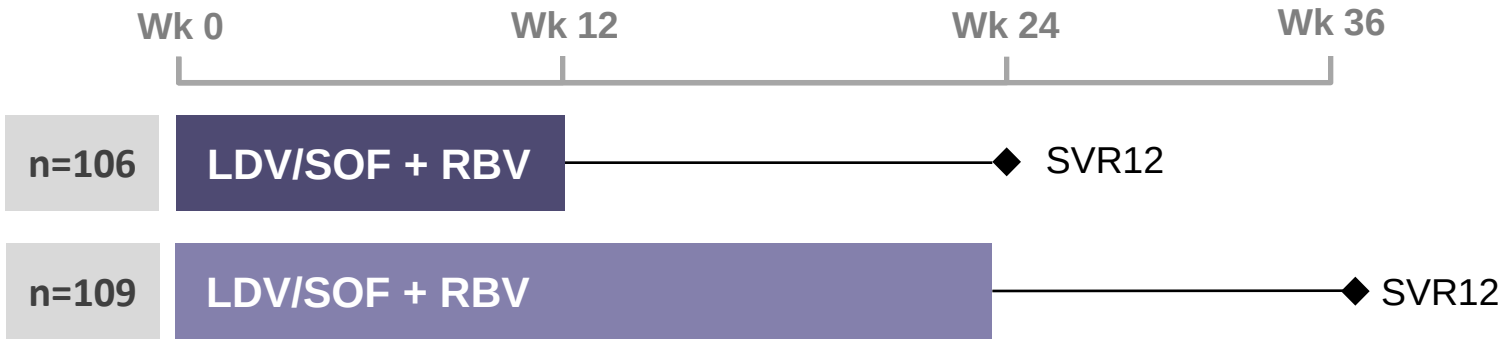
Charlton M et al, Gastro 2015 (SOLAR – 1)

Manns M et al, EASL 2015 (SOLAR – 2, submitted)

HARVONI® ledipasvir/sofosbuvir

SOLAR-1+2: LDV/SOF + RBV in Decompensated Cirrhosis

Study Design (n=215)



- 215 patients randomized 1:1 to 12 or 24 weeks of treatment
- GT 1 (n=202, 94%) or 4 (n=13, 6%) treatment-naïve or -experienced patients with decompensated cirrhosis CPT class B (n= 115) or C (n=100)
- Broad inclusion criteria
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, hemoglobin ≥ 10 g/dL
  - CL_{cr} ≥40 mL/min, platelets >30,000 x 10^3/μL
- **Stratified by CPT class B [score 7-9] or C [score 10–12]***
- **Ribavirin dosing: escalating dose (600 – 1200 mg/d)**

*Patients with CPT scores 13-15 excluded.

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Demographics (n= 108)

	CTP B		CTP C	
	12 Weeks n=30	24 Weeks n=29	12 Weeks n=23	24 Weeks n=26
Median age, y (range)	60 (53-63)	58 (56-62)	58 (53-61)	59 (55-62)
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (91)	24 (92)
BMI ≥30 kg/m^2, n (%)	10 (33)	10 (34)	13 (57)	9 (35)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	5.9 ± 0.7	5.8 ±0.8	5.6 ±0.6	5.8 ±0.7
GT 1a, n (%)	19 (63)	22 (76)	15 (65)	18 (69)
IL28B non-CC, n (%)	26 (87)	23/28 (82)	17 (74)	19 (73)
Prior HCV treatment, n (%)	22 (73)	19 (66)	11 (48)	18 (69)
MELD score, n (%)				
<10	6 (20)	8 (28)	0	0
10–15	21 (70)	16 (55)	16 (70)	13 (50)
16-20	3 (10)	5 (17)	7 (30)	12 (46)
21-25	0	0	0	1 (4)
Ascites, n (%)	17 (57)	17 (59)	22 (96)	25 (96)
Encephalopathy, n (%)	20 (67)	16 (55)	21 (91)	23 (88)

SOLAR-1 vs SOLAR-2: GT 1a 74% vs 47%; GT 4 1% vs 9%

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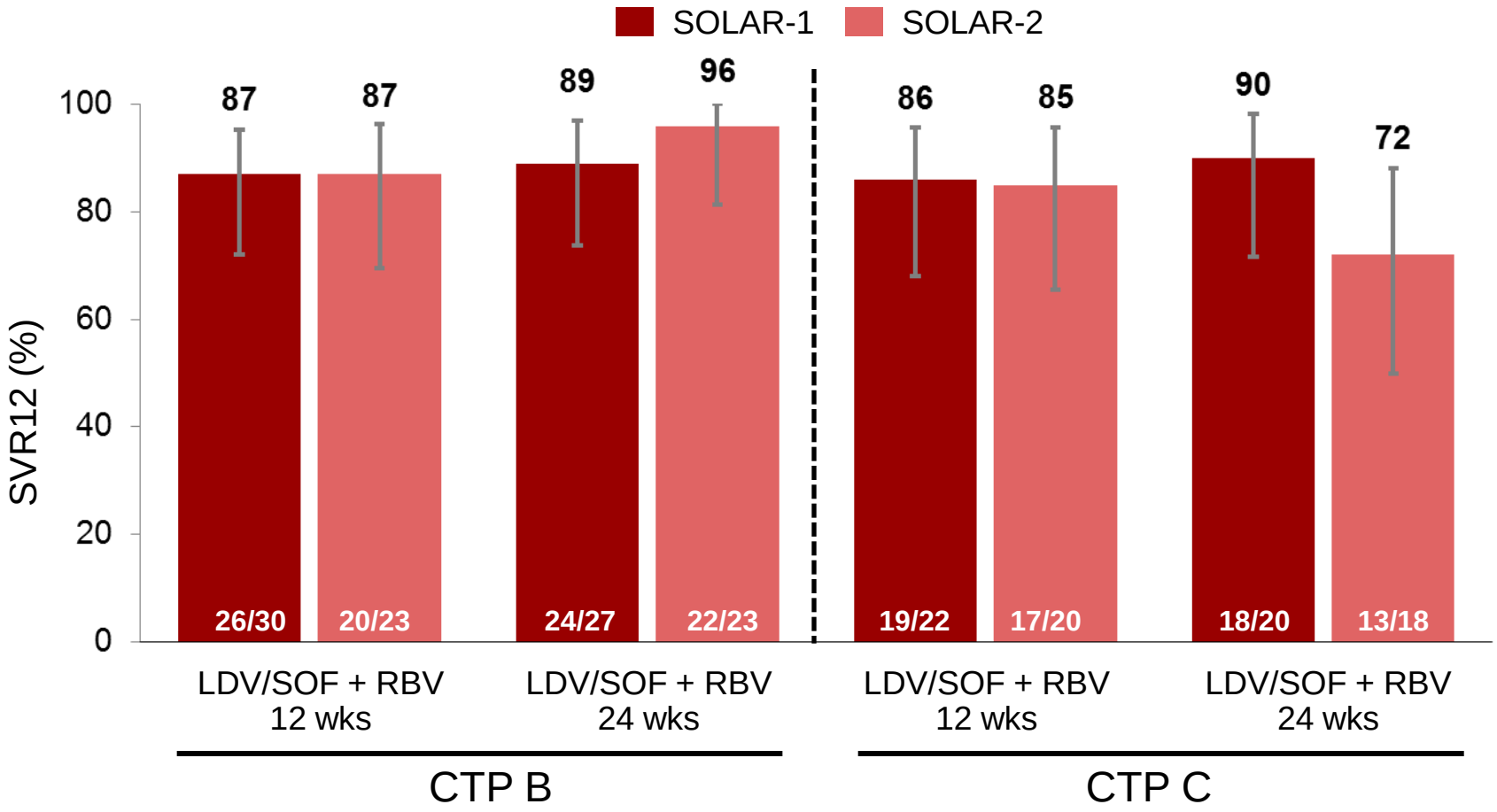
Charlton M et al, Gastro 2015

HARVONI® ledipasvir/sofosbuvir

SOLAR-1 and SOLAR-2: LDV/SOF + RBV in Decompensated Cirrhosis

Overall Efficacy Pre-Transplant

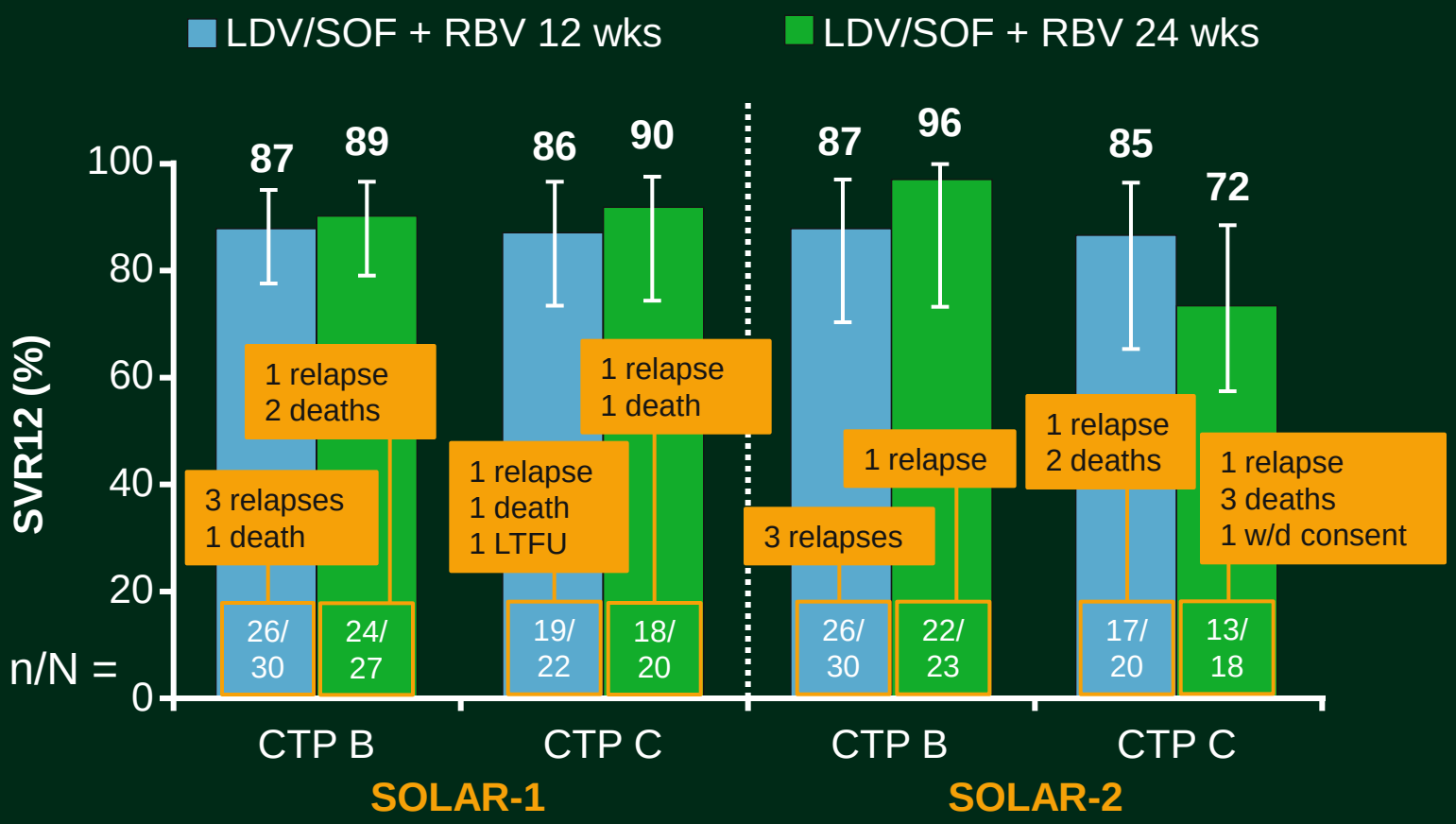


Comparable efficacy between SOLAR-1 and SOLAR-2 studies

Error bars represent 90% confidence intervals.

Flamm, AASLD, 2014, Oral #239; Manns, EASL, 2015, GO2

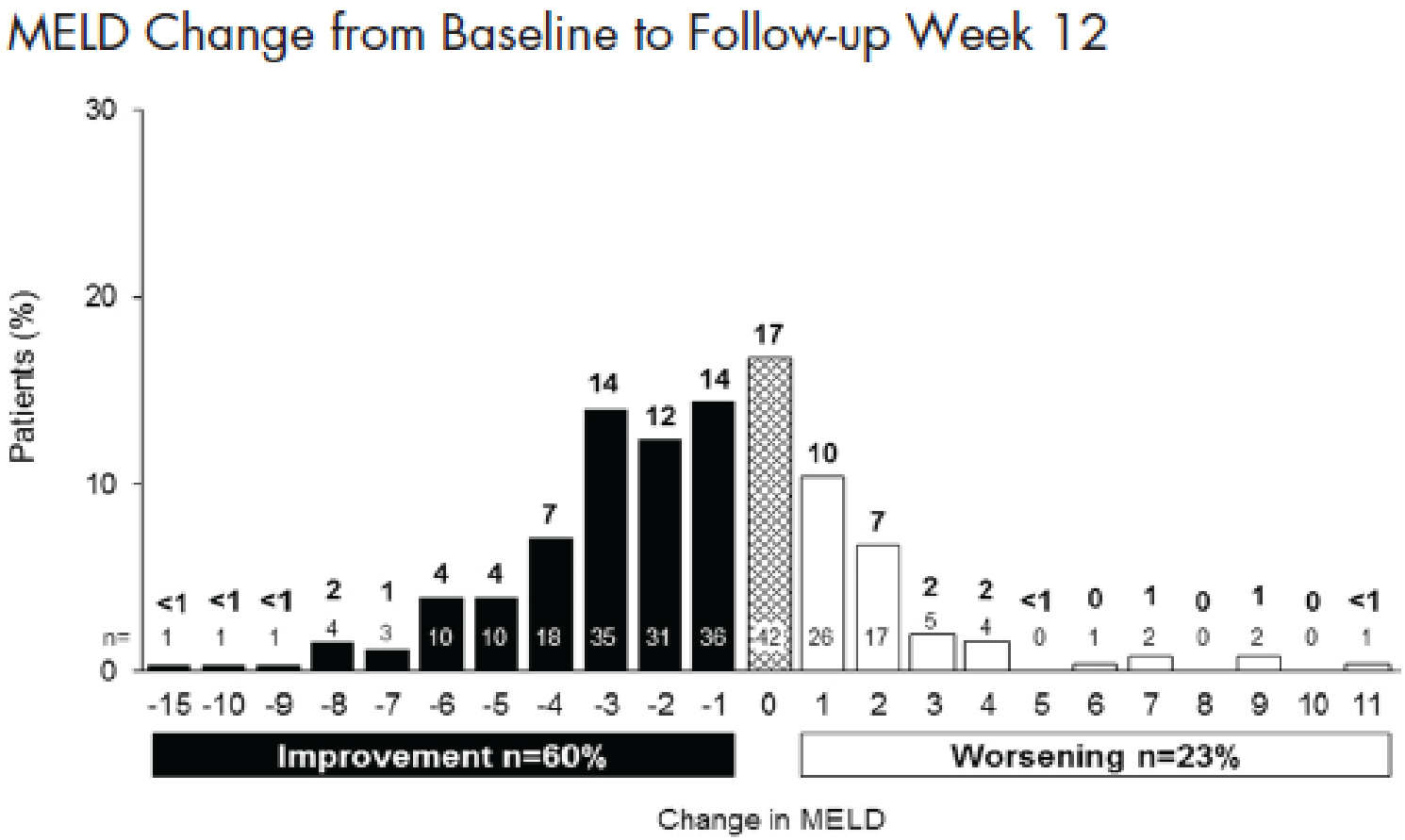
SOLAR-1 and -2: Causes of Virological Failure in decompensated cirrhosis



24 virological failures: 12 relapses, 10 deaths, 1 consent w/d, 1 LTFU

Charlton M et al, Gastro 2015. Manns M et al. EASL 2015.

SOLAR-1+2 : LDV/SOF + RBV in decompensated pre/post-OLT patients (n=250)*



* 250 decompensated patients who had achieved SVR12

Gane E et al, AASLD 2015

SOLAR-1+2. LDV/SOF + RBV in Decompensated Cirrhosis

Conclusions

- LDV/SOF + RBV for 12 weeks resulted in a high SVR12 rate in HCV subjects decompensated cirrhosis
  - Relapse rates were similar to relapse rates in subjects with compensated cirrhosis
  - Extending treatment duration to 24 weeks did not increase the response rate
- Virologic response was associated with improvements in bilirubin, albumin, MELD and CTP scores in both CTP class B and C subjects

Flamm, AASLD, 2014, Oral #239

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HARVONI® ledipasvir/sofosbuvir

Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With post-transplant recurrence

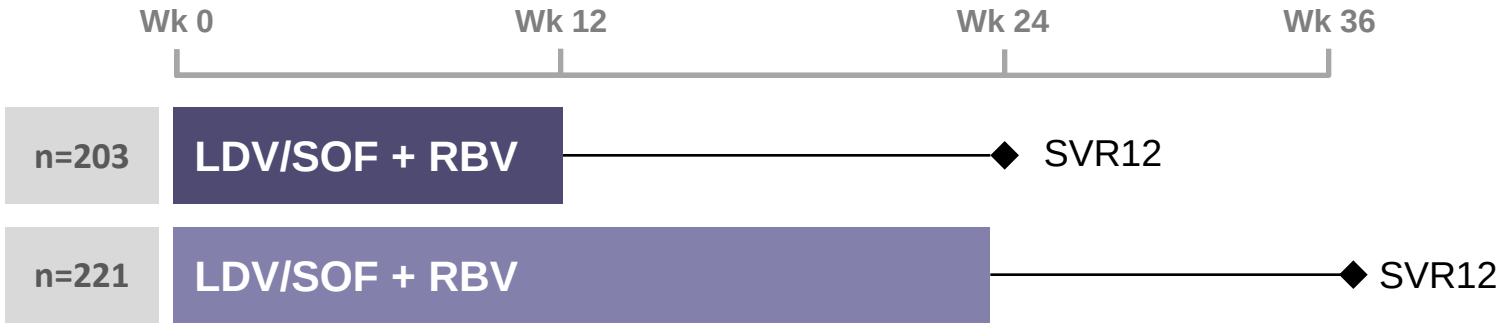
Charlton M et al, Gastro 2015 (SOLAR – 1)

Manns M et al, EASL 2015 (SOLAR – 2)

HARVONI® ledipasvir/sofosbuvir

SOLAR-1+2: LDV/SOF + RBV in post-LT recurrence

Study Design n=424



- **424 patients randomized 1:1 to 12 or 24 weeks of treatment**
- **GT 1 (n=395, 93%) or 4 (n=29, 7%) treatment-naïve or -experienced post-transplant patients**
- Broad inclusion criteria
  - Total bilirubin ≤10 mg/dL, hemoglobin ≥10 g/d, platelets >30 x 10^3/µL
  - CL_{cr} ≥40 mL/min
  - ≥3 months from liver transplant
  - No hepatocellular carcinoma
- **Stratified at screening: F0–F3, CPT A, B, C**
- **RBV dosing**
  - **F0–F3 and CPT A cirrhosis: weight-based**
  - **CPT B and C cirrhosis: dose escalation, 600–1200 mg/d**

SOLAR-1. LDV/SOF + RBV in post-LT recurrence ‡

Demographics (n=223)

	F0-F3 n=111	CTP A n=51	CTP B n=52	CTP C n=9
Median age, y (range)	59 (26-72)	60 (21-81)	61 (37-72)	60 (57-66)
Male, n (%)	91 (82)	41 (80)	45 (87)	9 (100)
White, n (%)	99 (89)	41 (80)	45 (87)	8 (89)
Median HCV RNA, $\log_{10}$ IU/mL (range)	6.6 (2.4-7.8)	6.6 (4.6-7.6)	6.4 (4.4-7.2)	6.3 (5.8-6.8)
GT 1a, n (%)	80 (72)	34 (67)	38 (73)	7 (78)
IL28B non-CC, n (%)	90 (81)	43 (84)	44 (85)	6 (67)
Median years from OLTx (range)	2.9 (0.4-18.2)	8.1 (0.8-23.3)	5.6 (0.9-22.5)	5.2 (1.2-15.5)
Prior HCV treatment, n (%)	87 (78)	46 (90)	44 (85)	8 (89)
MELD (n, %)				
<10	N/A	28 (55)	13 (25)	1 (11)
10-15	N/A	20 (39)	33 (63)	5 (56)
16-20	N/A	3 (6)	4 (8)	2 (22)
21-25	N/A	0	2 (4)	1 (11)
Ascites, n (%)	2 (2)	2 (4)	40 (77)	9 (100)
Encephalopathy, n (%)	1 (1)	3 (6)	23 (44)	7 (78)

SOLAR-1 vs SOLAR-2: GT 1a 72% vs 50%; GT 4 1% vs 12%

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Reddy, AASLD, 2014, Oral #8

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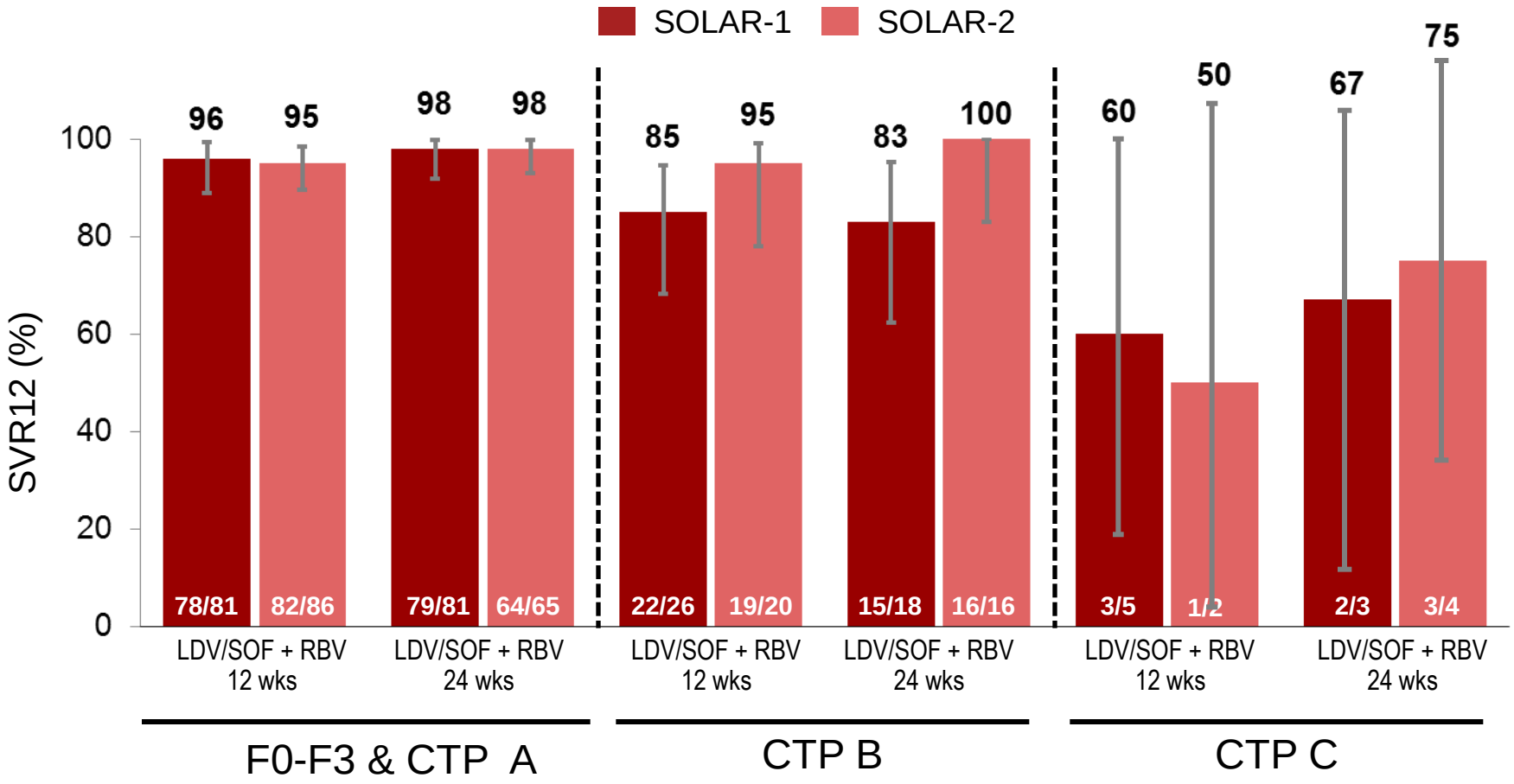
Overall Efficacy Post-Transplant

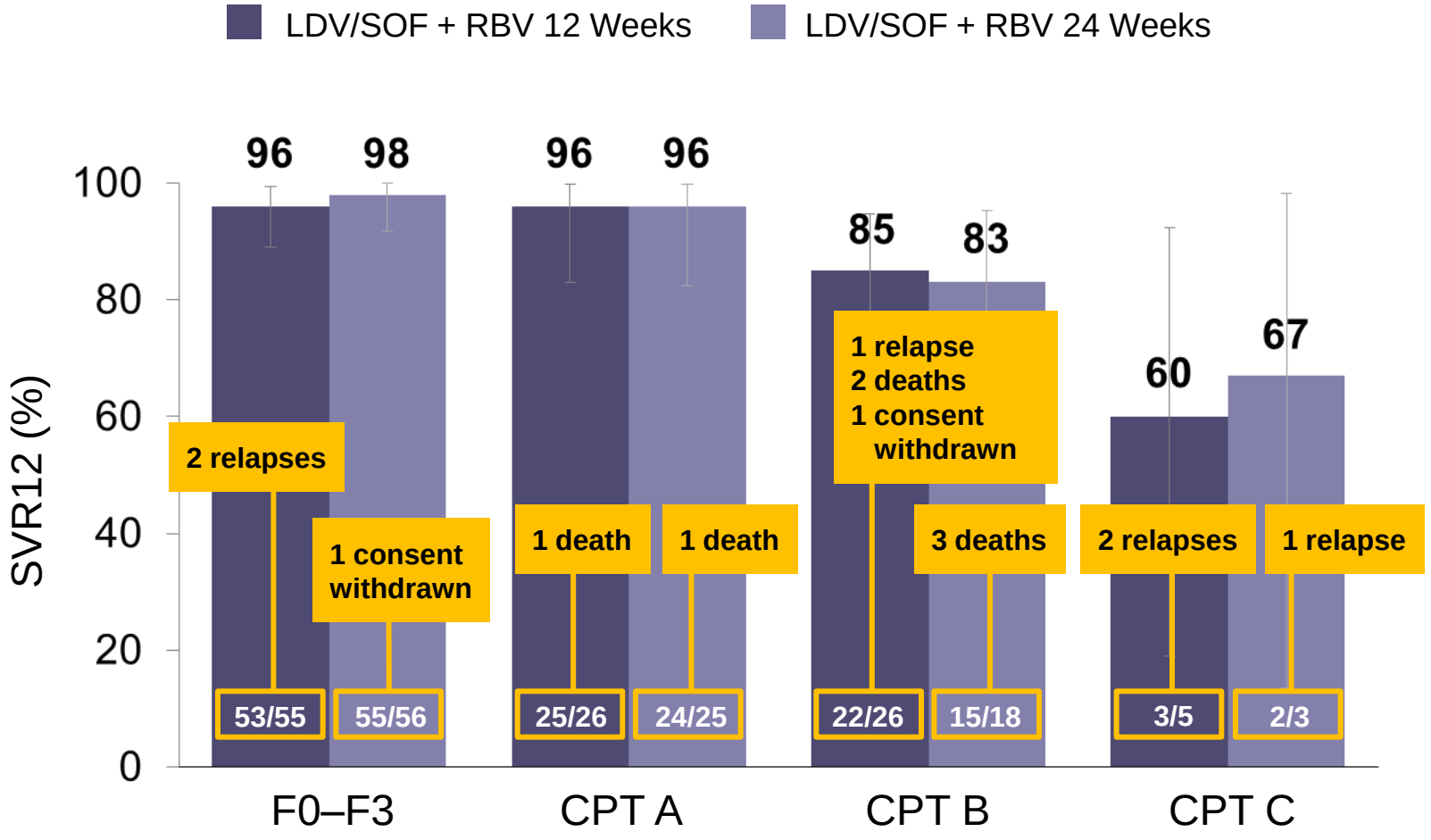


Comparable efficacy between SOLAR-1 and SOLAR-2 studies

Reddy, AASLD, 2014, Oral #8; Manns, EASL, 2015, GO2

SOLAR-2: SVR12

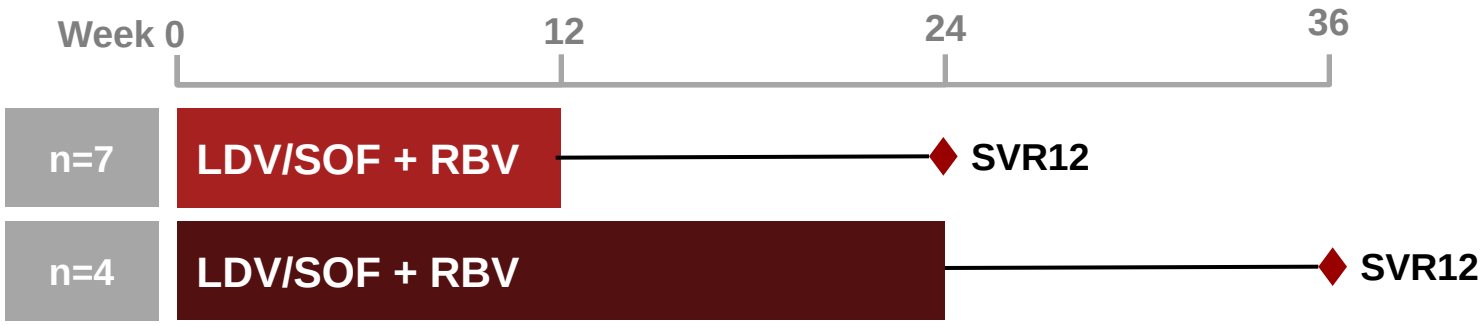
GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C



15 virological failures: 6 relapses, 7 deaths, 2 consent w/d

SOLAR-1 and SOLAR-2: Fibrosing Cholestatic Hepatitis (US and EU)

LDV/SOF+RBV for Treatment of FCH After Liver Transplantation (GT1)

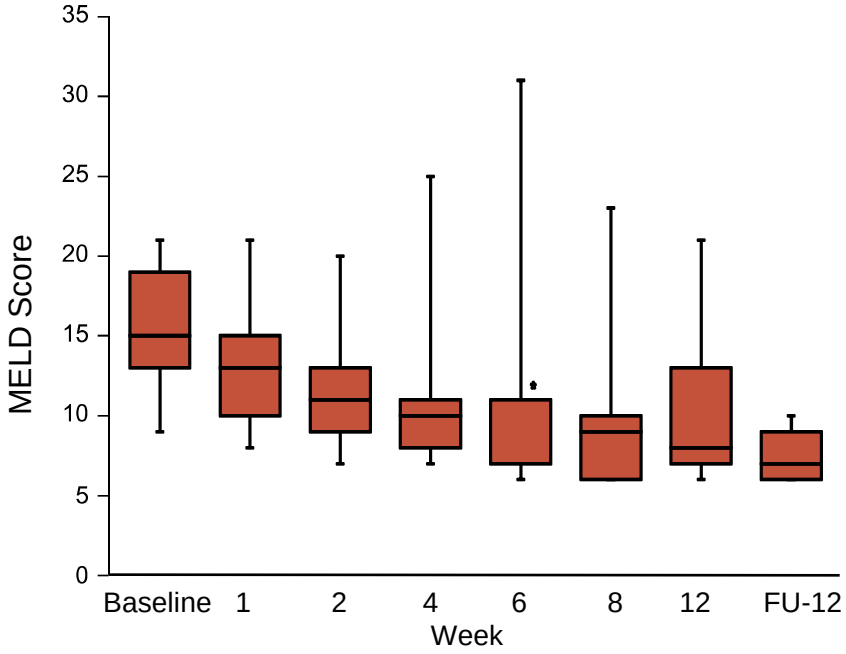


	12 Weeks LDV/SOF+RBV n=7	24 Weeks LDV/SOF+RBV n=4
Median age, y (range)	59 (56–65)	56 (52–64)
Male, n (%)	6 (86)	3 (75)
Median HCV RNA, log_{10} IU/mL (range)	6.6 (4.9–8.0)	6.4 (5.8–7.7)
Median years from transplant (range)	1.0 (0.4–1.6)	0.3 (0.2–0.4)
Median ALT, IU/L (range)	174 (71–211)	165 (62–220)
Median CL_{cr}, mL/min (range)	89 (36–94)	75 (69–103)

All 11 (100%) patients achieved SVR12

Forns, EASL, 2015

Liver Function and Safety Summary



*Median and third quartile MELD=11 at Week 6. One patient taking warfarin had MELD values at Weeks 4, 6, 8 and 12 only. Data represent median, quartile (Q)1 and Q3, and minimum and maximum values.

	12 Weeks LDV/SOF+RBV n=7	24 Weeks LDV/SOF+RBV n=4
AE	7 (100)	4 (100)
Grade 3–4 AE	1 (14)	1 (25)
Serious AE	3 (43)	2 (50)
D/C due to AE	0	0
Treatment-related SAE*	0	1* (25)

*Grade 2 dyspnea related to RBV treatment

Death, graft loss, and rejection were not observed

- Virologic response was associated with rapid and sustained improvements in liver function as assessed by MELD score
  - Most patients had total bilirubin, GGT, ALT levels within normal range at FU week 12

Forns, EASL, 2015

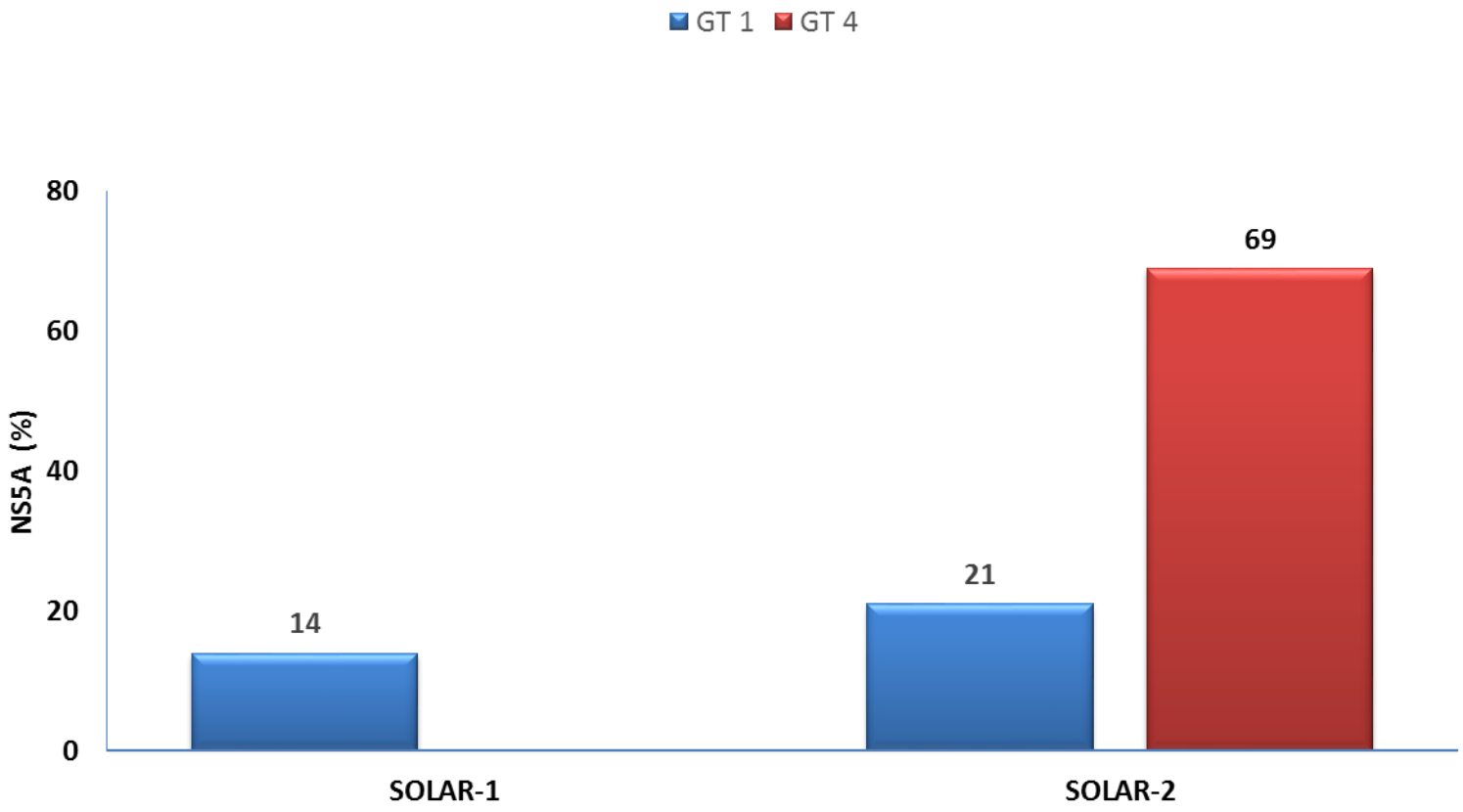
SOLAR-1+2: LDV/SOF + RBV in post-LT recurrence

Conclusions

- In subjects with recurrent HCV post transplantation, treatment with LDV/SOF+RBV for 12 or 24 weeks resulted in:
  - High rates of SVR12, irrespective of disease severity or duration of therapy (ie, 12 = 24 weeks)
  - Early post-treatment improvements in bilirubin and albumin
  - Decreases in MELD scores
  - 100% success rate in patients with CFH
- No on-treatment virologic failure

Reddy, AASLD, 2014, Oral #8

VARs NS5A basales en GT 1 y GT 4: Impacto sobre la recidiva



- SOLAR 1+2: Recidiva VARs NS5A basal vs no VARs: 5% vs 3%
- Ninguno de los 50 ptes con VARs NS5A basal que recibieron LDV/SOF 24 sem tuvo recidiva

Charlton M et al, Gastro 2015
Manns M et al, EASL 2015

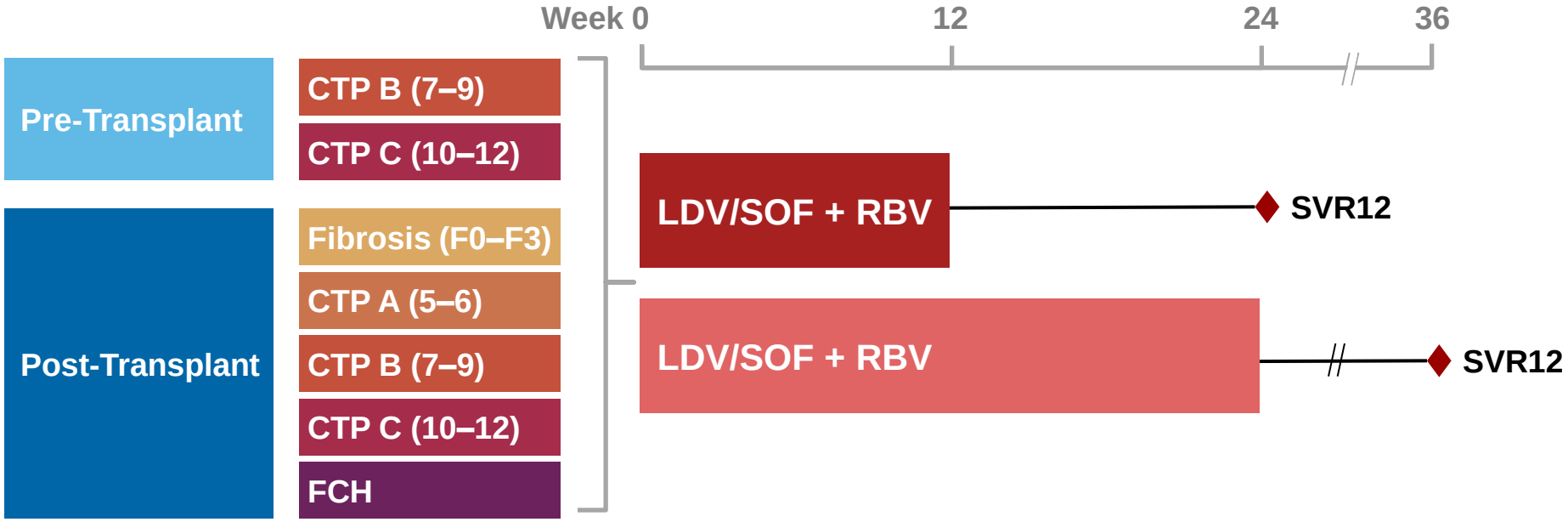
SOLAR 1 y 2: Recidiva virológica

- SOLAR-1
  - Recidiva: 13 (4%)
  - 11/13 (85%) de los ptes con recidiva tenían VARs NS5A
  - No VARs a sofosbuvir
  - 11/13 (85%) de los ptes tenían cirrosis descompensada
- SOLAR-2
  - Recidiva: 10 (3%)
  - Todos los ptes con recidiva tenían VARs NS5A
  - No VARs a sofosbuvir
  - 9/10 (90%) de los ptes con recidiva tenían cirrosis descompensada
  - Recidiva más frecuente en: cirrosis descompensada (5,7% vs 0,6%), GT 4 (8% vs 2%) y 12 sem (4,8 vs 1,2%)

Charlton M et al, Gastro 2015
Manns M et al, EASL 2015

Study Design

Pooled safety analysis of 659 patients from SOLAR-1 and -2 (US and EU)



- Broad inclusion criteria:
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤ 10 mg/dL, Haemoglobin ≥ 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, 600–1200 mg/d

Samuel, EASL, 2015, P0774

Overall Safety Summary

Patients, n (%)	Pre-Transplant	Post-Transplant		Total
	CTP B + C n=215	F0–3 + CTP A n=330	CTP B + C n=114	n=659
Any AE	208 (97)	316 (96)	109 (96)	**633 (96)**
Grade 3–4 AE	51 (24)	76 (23)	33 (29)	**160 (24)**
Serious AE	61 (28)	49 (15)	34 (30)	**144 (22)**
Serious treatment-related AE	5 (2)	10 (3)	4 (4)	**19 (3)**
AE leading to D/C of LDV/SOF	9 (4)	5 (2)	5 (4)	**19 (3)**
Death	10 (5)	4 (1)	6 (5)	**20 (3)**
Rejection episode	0	1	0	**1**
Graft loss	1	1	0	**2**
Liver transplantation	11	0	0	**11**

- Treatment-related SAEs were mostly related to RBV treatment
- Deaths and AEs that led to D/C of LDV/SOF were not attributed to study treatment

SOLAR-1/2 – Deaths On Study

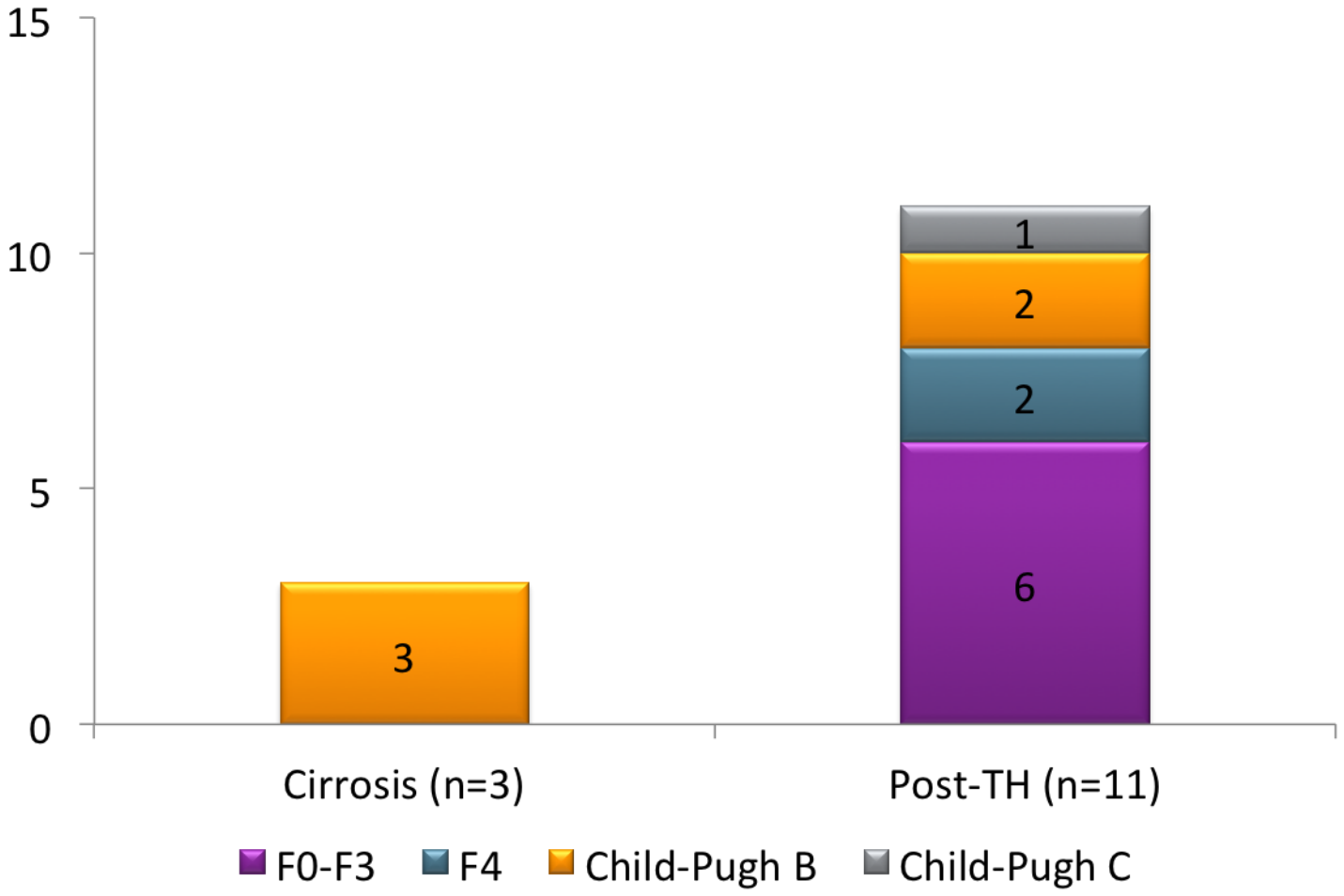
	Cause of Deaths (n=20, 3%)	Population	
Did not complete treatment	Septic shock	Pre	CPT B
	Cardiac arrest in setting of sepsis	Pre	CPT B
	Oliguric renal failure	Pre	CPT C
	Septic shock	Pre	CPT C
	Gastrointestinal bleeding and liver failure	Pre	CPT C
	Multiorgan failure and septic shock	Pre	CPT C
	Cardiac arrest due to ischemic heart disease	Pre	CPT C
	Staphylococcus aureus sepsis	Pre	CPT C
	Gastrointestinal bleeding and liver failure	Post	CPT A
	Progressive multifocal leukoencephalitis	Post	CPT A
	Thoracic aorta aneurysm dissection	Post	CPT B
	Internal bleeding	Post	CPT B
	Multiorgan failure with sepsis	Post	CPT B
	Multiorgan failure due to decompensated cirrhosis	Post	CPT B
	Infiltrative multifocal hepatocarcinoma	Post	CPT C
	Intestinal ischemia	Post	CPT C
Died ≤30 days after completing treatment	Sepsis and multiorgan failure	Pre	CPT B
	Liver failure due to chronic liver rejection	Post	F0-F3
	Myocardial infarction	Post	CPT A
	Multiorgan failure due to decompensated cirrhosis	Post	CPT C

Deaths were consistent with disease progression

Samuel, EASL, 2015, P0774

SOLAR-2. HUP La Fe

SOLAR-2. HUP La Fe. Población de estudio (n=14)

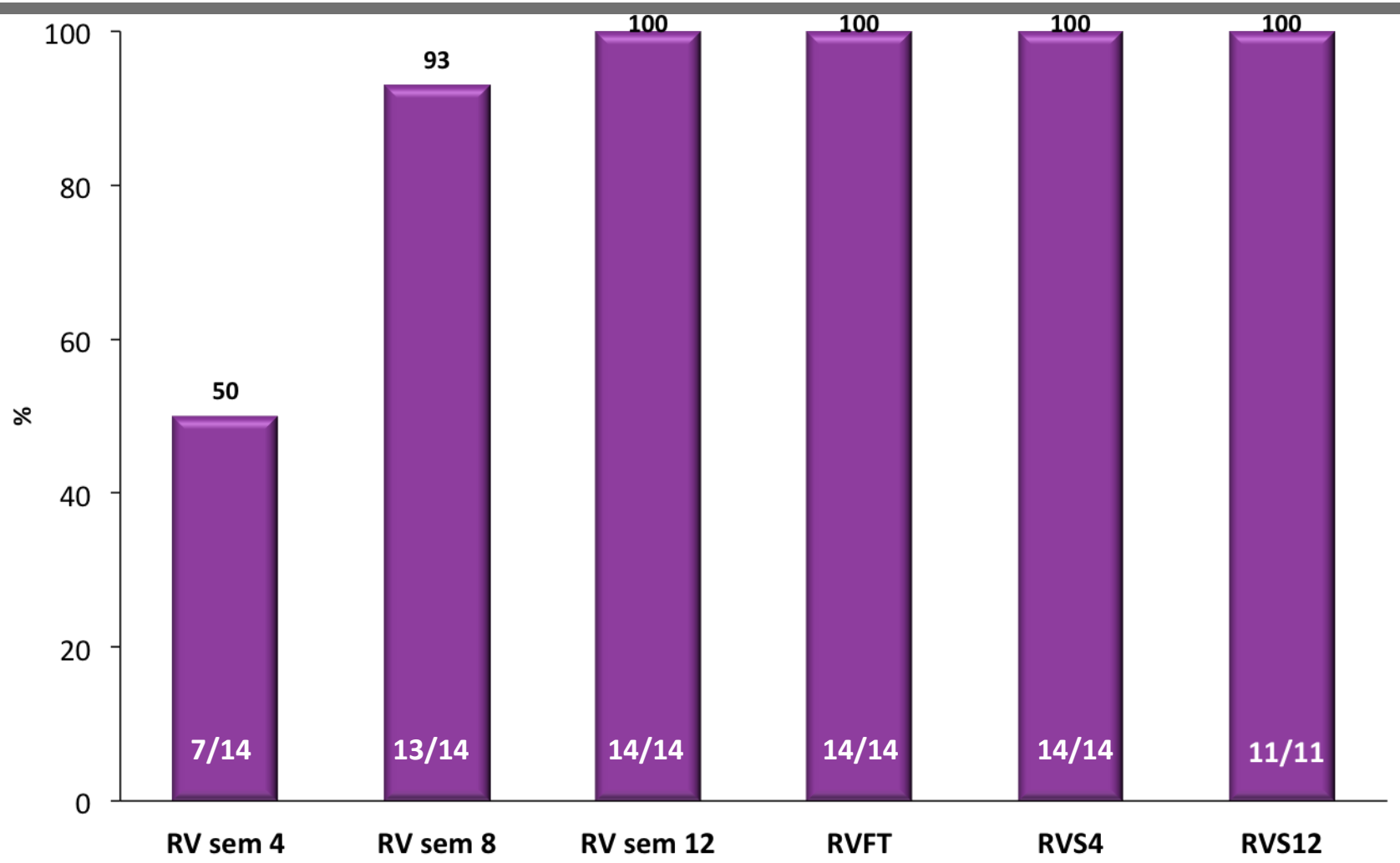


SOLAR-2. HUP La Fe. Características demográficas

	n=14
Edad (años), mediana (rango)	62 (43-75)
Hombres, n (%)	11 (79)
IMC ≥30, n (%)	6 (43)
Genotipo 1, n (%)	13 (93)
IL28 no CC, n (%)	10 (71)
Tratº previo, n(%)	8 (57)
ARN VHC log UI/mL , mediana (rango)	6,5 (3,4-8,3)
MELD, mediana (rango)*	12 (7-19)
Ascitis, n (%)*	2 (25)
Encefalopatía*, n (%)	1 (12)
Tº desde el TH (años), mediana (rango)**	10,4 (1,4-17)
Duración 12/24 sem, n	5/9

*sólo en cirrosis pre/post-TH (n=8), **sólo en post-TH (n=11)

SOLAR-2. HUP La Fe. Respuesta virológica global (ITT)



Recomendaciones GPC EASL en pacientes con indicación de TH

Genotipo	Cirrosis compensada	Cirrosis descompensada (CP B-C)
G 1	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**
G 2	-	-
G 3	-	-
G 4	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**
G 5/6	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**

EASL Recommendations on treatment of hepatitis C 2015. April 2015

Recomendaciones GPC EASL en Hep C recurrente

Genotipo	No cirrosis y Cirrosis compensada	Cirrosis descompensada (CP B-C)
G 1	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**
G 2	-	-
G 3	-	-
G 4	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**
G 5/6	**SOF/LDV + RBV 12 sem**	**SOF/LDV + RBV 12 sem**

EASL Recommendations on treatment of hepatitis C 2015. April 2015

- Gracias por su atención!!

HARVONI: ¿Seguimos teniendo poblaciones especiales?

Cirrótico descompensado y entorno del Trasplante

Martín Prieto
Unidad de Hepatología
HUP La Fe, Valencia

Agenda

- Introducción
- SOLAR 1 y 2
  - Cirrosis descompensada
  - Hepatitis C recurrente: enfermedad compensada y cirrosis descompensada
  - Hepatitis Colestásica fibrosante
  - Análisis de Seguridad

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HARVONI® ledipasvir/sofosbuvir

Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

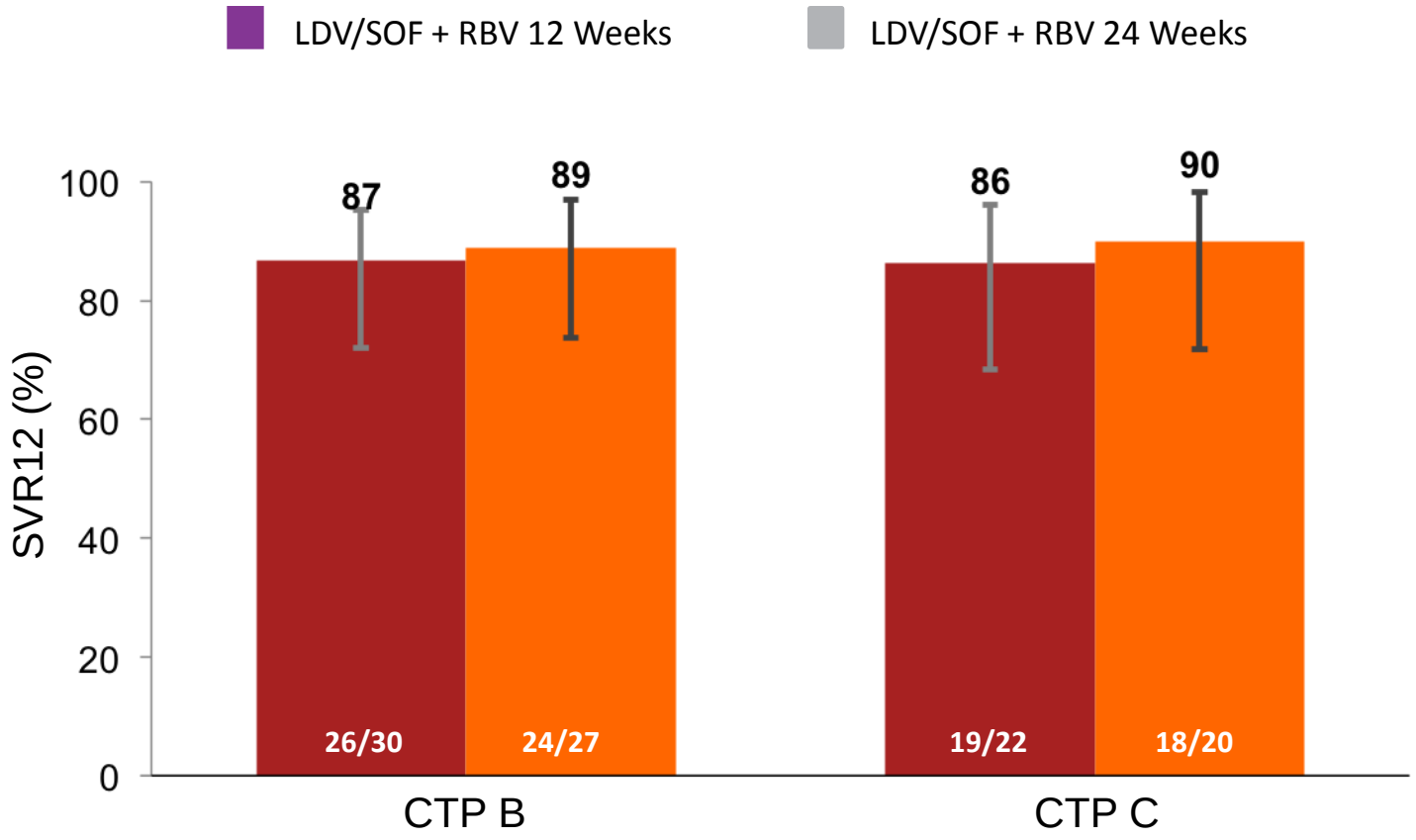
Steven L. Flamm[1], Gregory T. Everson[2], Michael R. Charlton[3], Jill M. Denning[4], Sarah Arterburn[4], Theo Brandt-Sarif[4], Phillip S. Pang[4], John G. McHutchison[4], K. Rajender Reddy[5], Nezam H. Afdhal[6]

[1]Northwestern Feinberg School of Medicine, Chicago, IL; [2]University of Colorado Denver, Aurora, CO; [3]Intermountain Medical Center, Murray, UT; [4]Gilead Sciences, Inc., Foster City, CA; [5]University of Pennsylvania School of Medicine, Philadelphia, PA; [6]Beth Israel Deaconess Medical Center, Boston, MA

AASLD 2014, Boston

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Results: SVR12



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

Error bars represent 90% confidence intervals.

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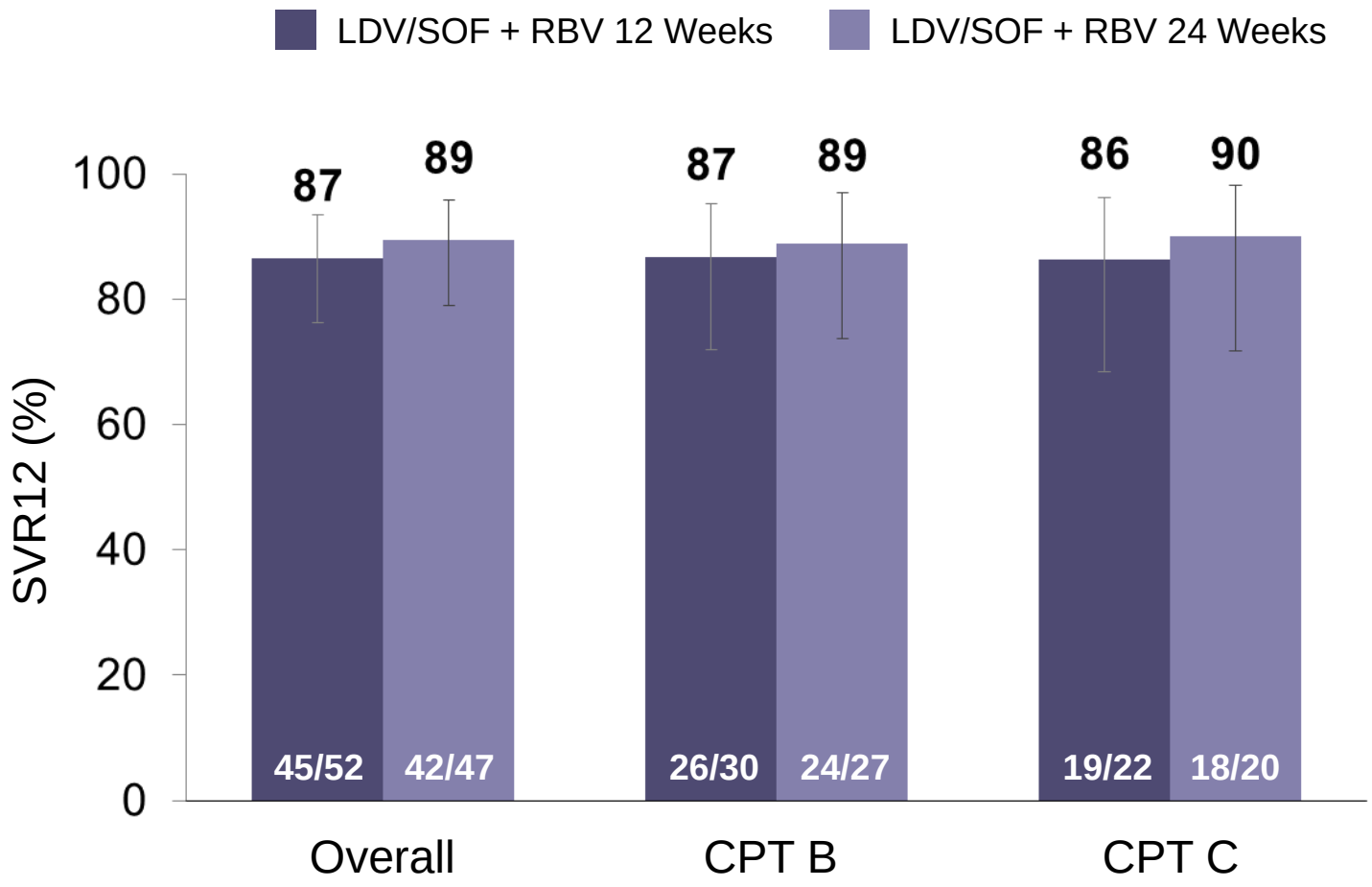
Flamm, AASLD, 2014, Oral #239

HARVONI® ledipasvir/sofosbuvir

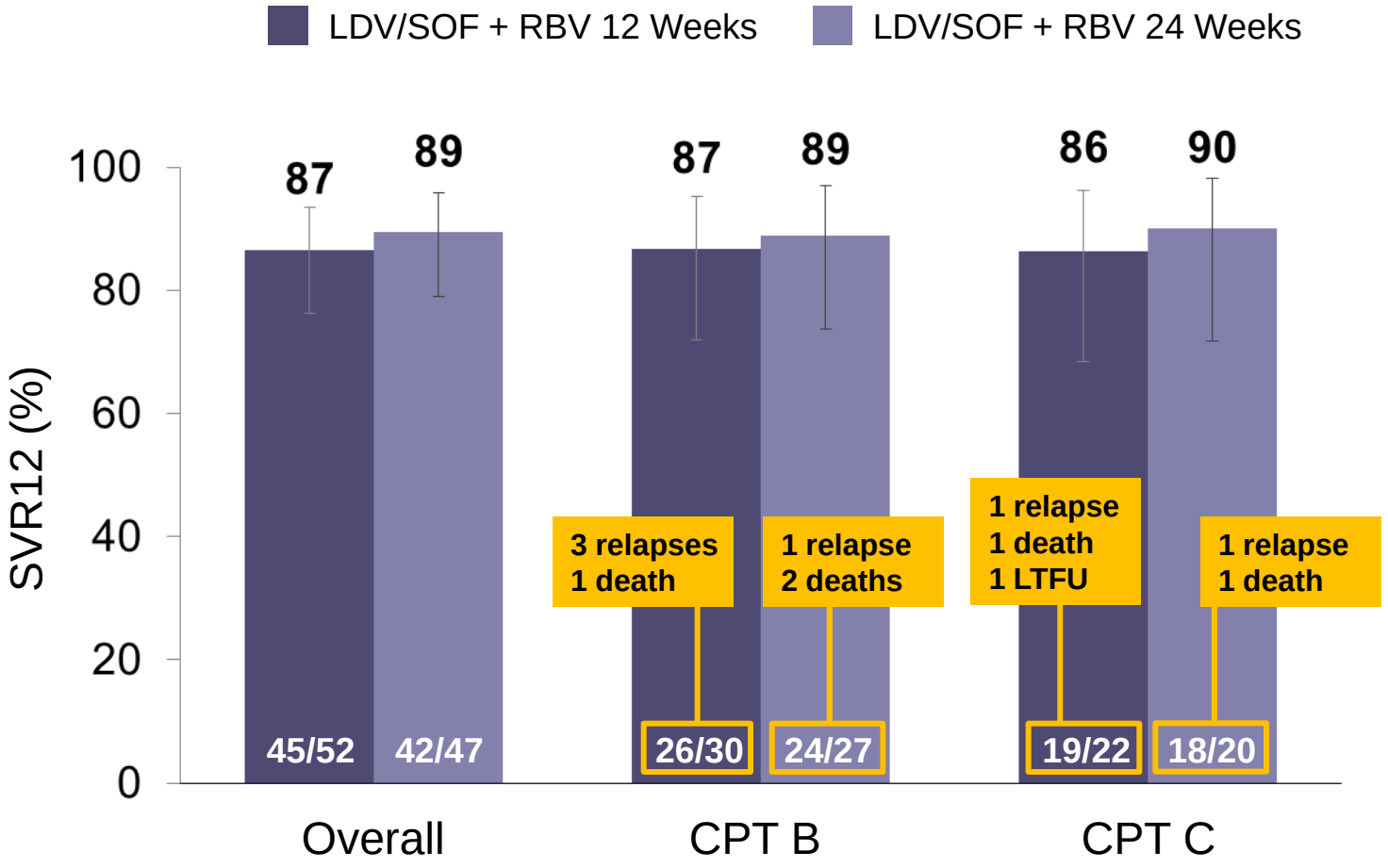
SOLAR-1. Results: SVR12

GT 1 and 4, CPT Class B and C



SOLAR-1. Results: SVR12

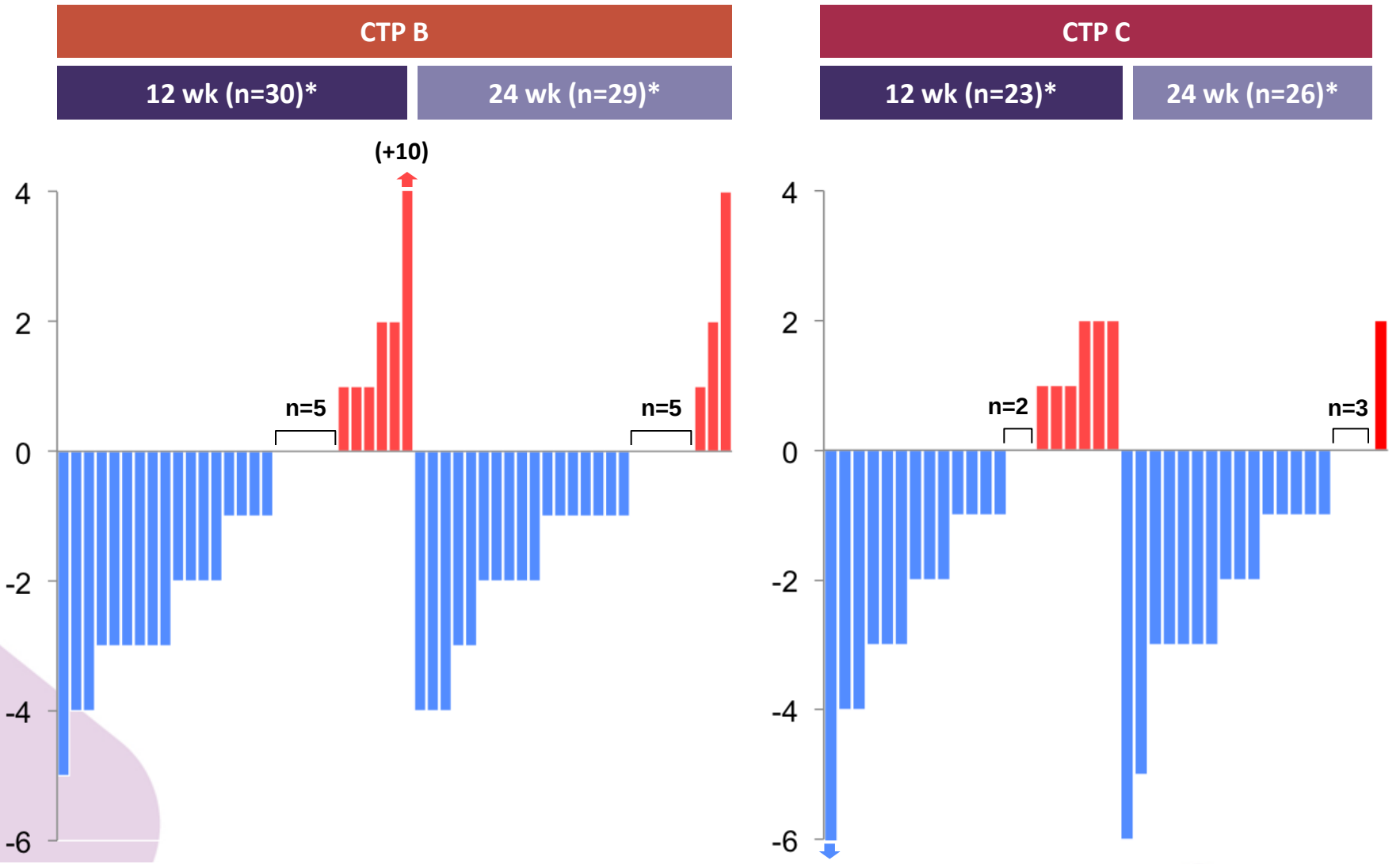
GT 1 and 4, CPT Class B and C



12 virological failures: 6 relapses, 5 deaths, 1 LTFU

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Results: MELD Change from BL to F-U Week 4



*Missing FU-4: n=2 CTP B 12 wk; n=4 CTP B 24 wk; n=2 CTP C 12 wk; n=7 CTP C 24 wk.

Flamm, AASLD, 2014, Oral #239

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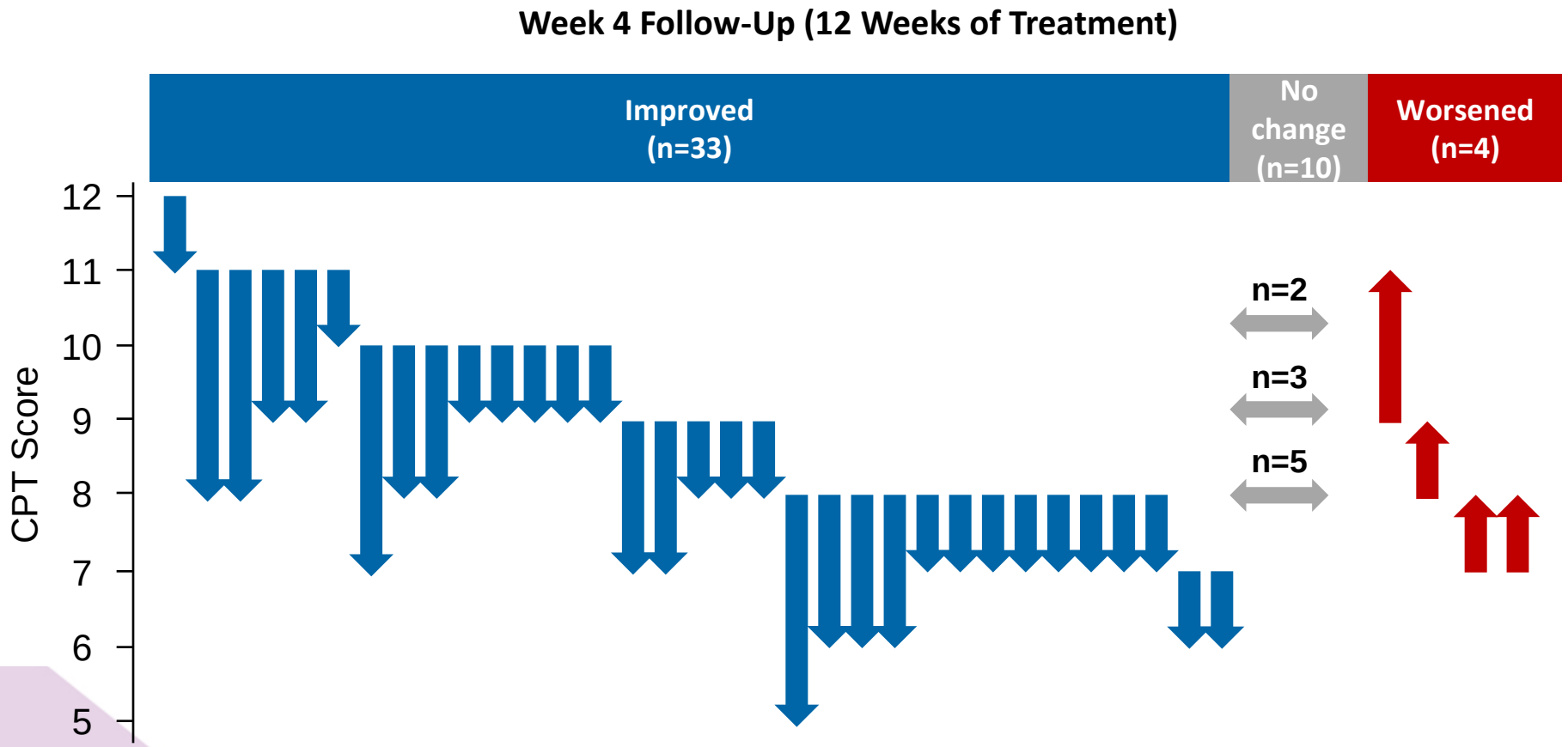
SOLAR-1. Results: CPT Scores

Change From Baseline to Follow-Up Week 4



Arrows represent individual patients.

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SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Results: Overall Safety Summary

Subjects, n (%)	CTP B		CTP C	
	12 Weeks n=30	24 Weeks n=29	12 Weeks n=23	24 Weeks n=26
Any AE	29 (97)	27 (93)	23 (100)	26 (100)
Grade 3/4 AE	2 (7)	8 (28)	6 (26)	11 (42)
SAEs	3 (10)	10 (34)	6 (26)	11 (42)
Tx Related SAEs	2 (7)	0	0	2 (8)
D/C due to AE	0	1 (3)	0	2 (8)
Death	1 (3)	2 (7)	2 (9)	1 (4)

Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Post-Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study

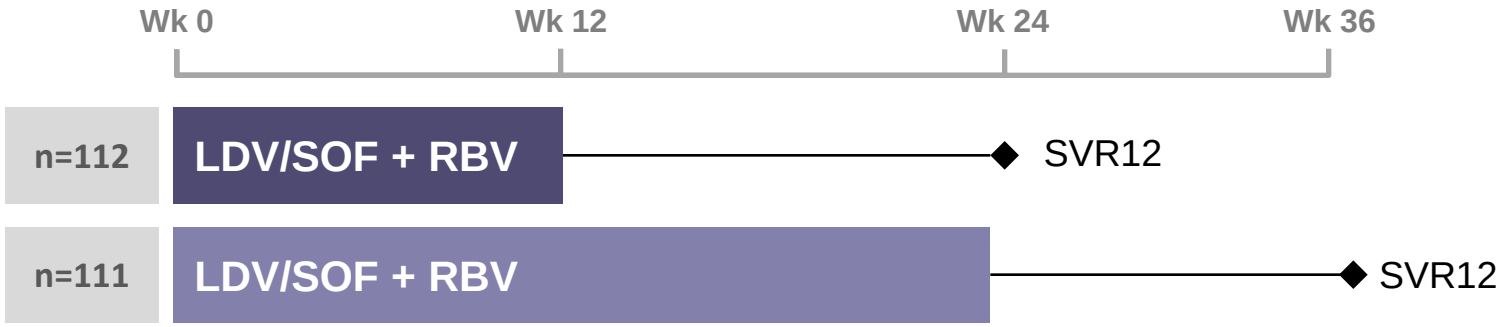
K. Rajender Reddy[1], Gregory T. Everson[2], Steven L. Flamm[3], Jill M. Denning[4], Sarah Arterburn[4], Theo Brandt-Sarif[4], Phillip S. Pang[4], Hadas Dvory-Sobol[4], John G. McHutchison[4], Michael P. Curry[5], Michael Charlton[6]

[1]University of Pennsylvania School of Medicine, Philadelphia, PA; [2]University of Colorado Denver, Aurora, CO; [3]Northwestern Feinberg School of Medicine, Chicago, IL; [4]Gilead Sciences, Inc., Foster City, CA; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Intermountain Medical Center, Murray, UT

AASLD 2014, Boston

SOLAR-1: LDV/SOF + RBV in post-LT recurrence

Study Design n=223



- **223 patients randomized 1:1 to 12 or 24 weeks of treatment**
- GT 1 or 4 treatment-naïve or -experienced post-transplant patients
- Broad inclusion criteria
  - Total bilirubin ≤10 mg/dL
  - Hemoglobin ≥10 g/dL
  - Platelets >30 x 10^3/µL
  - CL_{cr} ≥40 mL/min
  - ≥3 months from liver transplant
  - No hepatocellular carcinoma
- **Stratified at screening: F0–F3, CPT A, B, C**
- **RBV dosing**
  - **F0–F3 and CPT A cirrhosis: weight-based**
  - **CPT B and C cirrhosis: dose escalation, 600–1200 mg/d**

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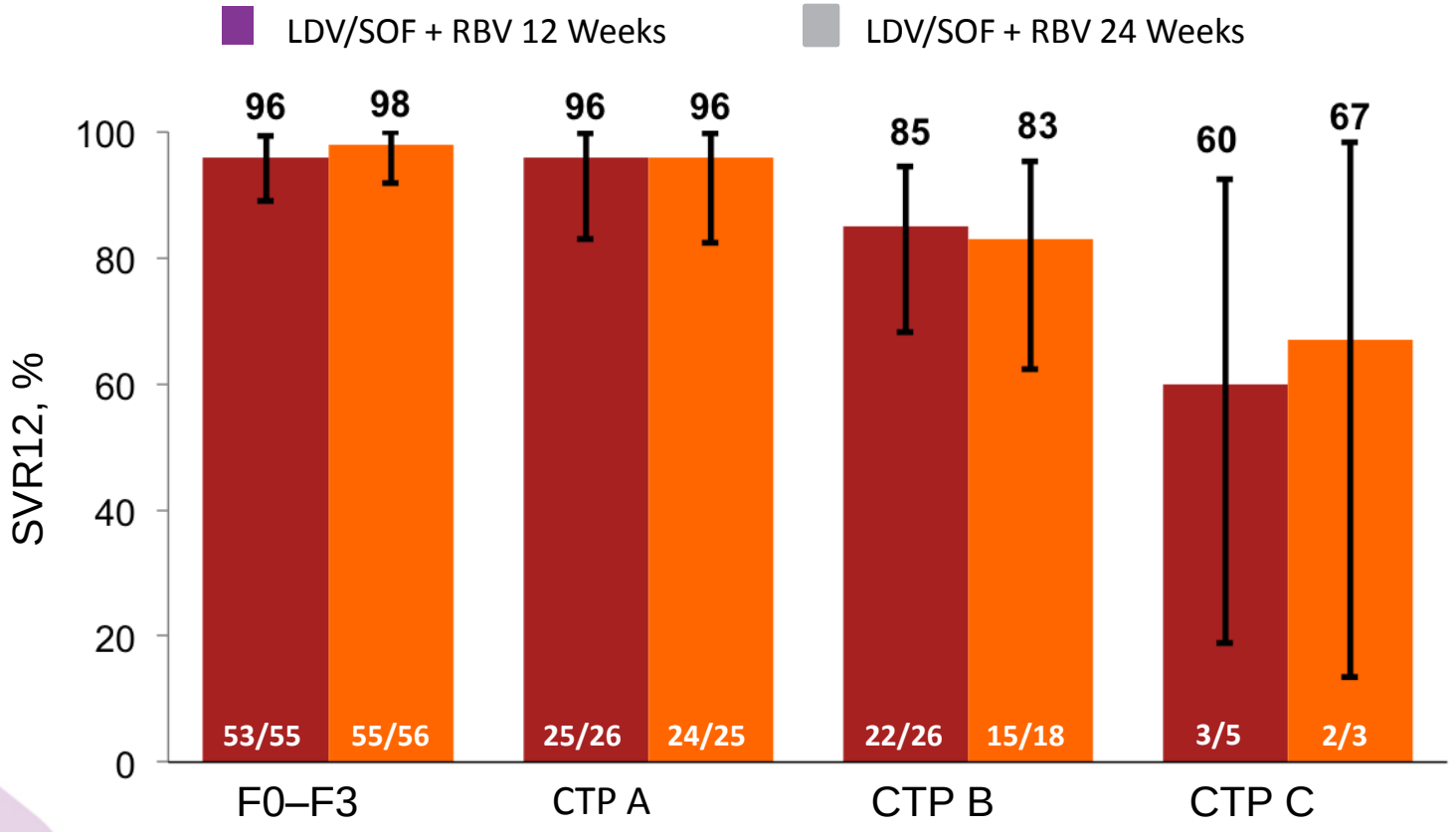
HARVONI® ledipasvir/sofosbuvir

SOLAR-1: LDV/SOF + RBV in post-LT recurrence

‡

Results: SVR12



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

Error bars represent 2-sided 90% exact confidence intervals.

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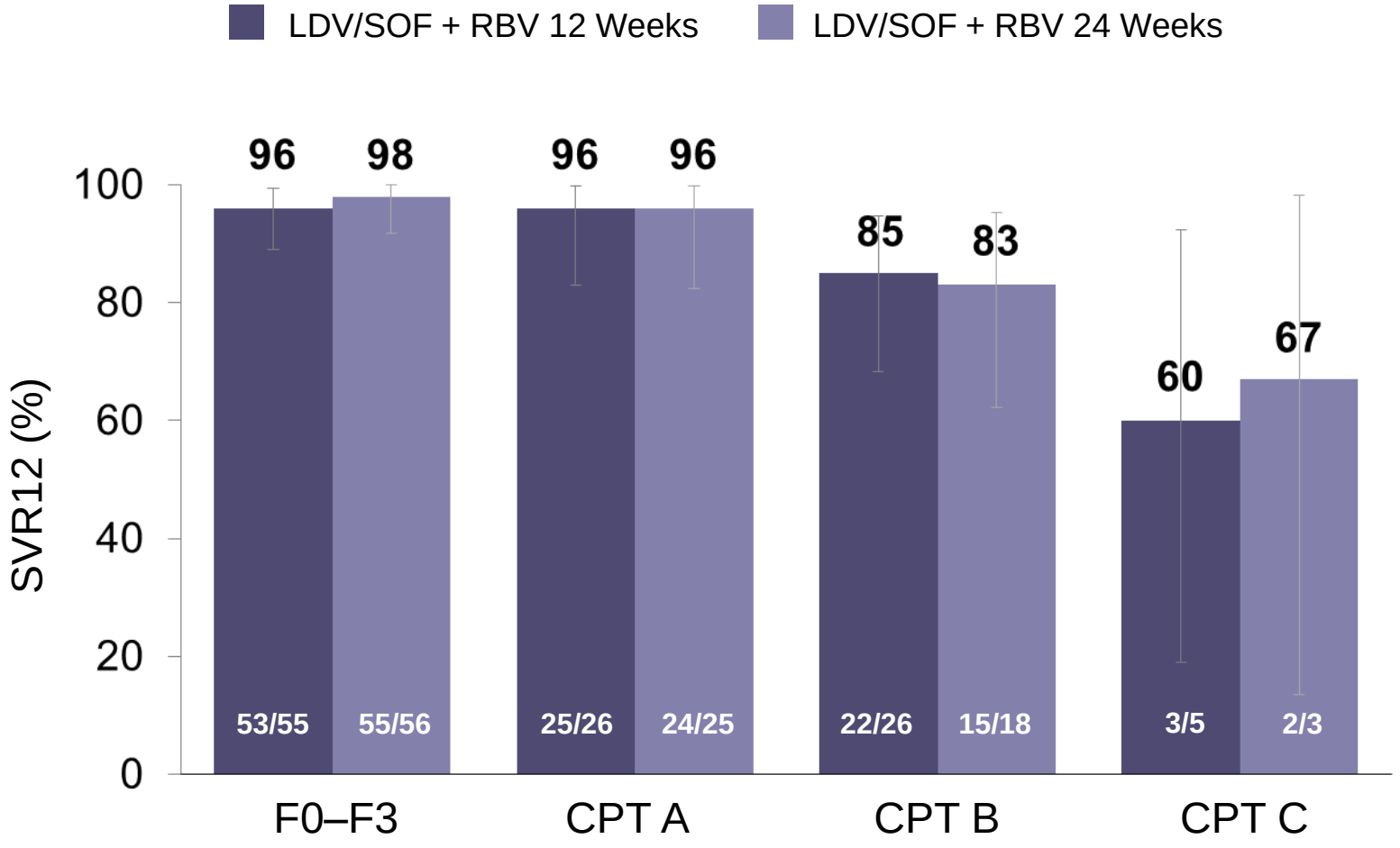
Reddy, AASLD, 2014, Oral #8

HARVONI® ledipasvir/sofosbuvir

Results: SVR12

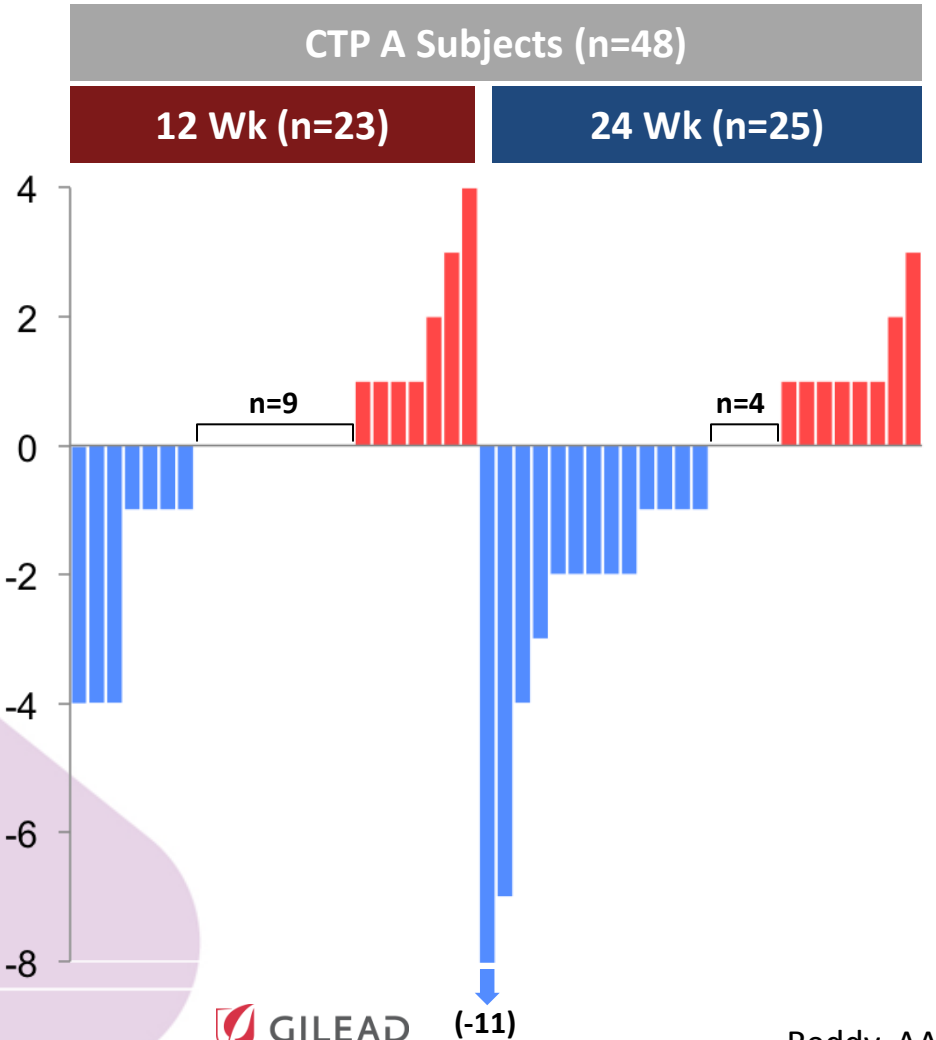
GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C

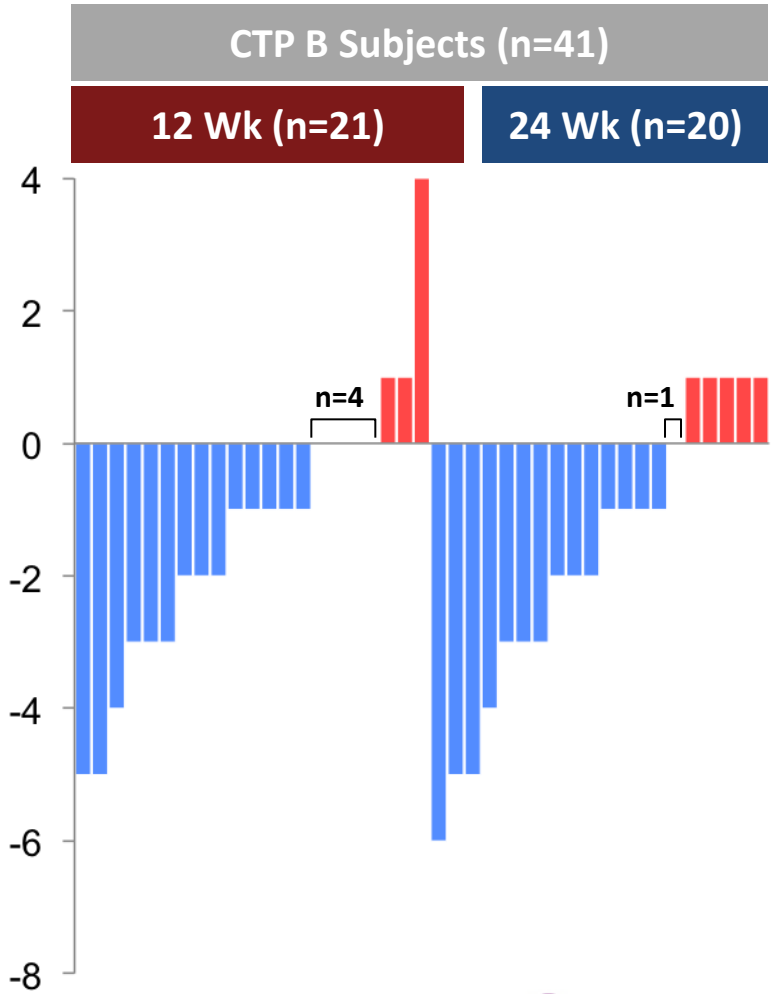


8 CPT B 24 Week and 1 CPT C 24 Week subjects have not reached the Week 12 post-treatment visit.
Error bars represent 2-sided 90% exact confidence intervals.

SOLAR-1: LDV/SOF + RBV in post-LT recurrence ‡

Results: MELD Change from BL to F-U Week 4





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Reddy, AASLD, 2014, Oral #8

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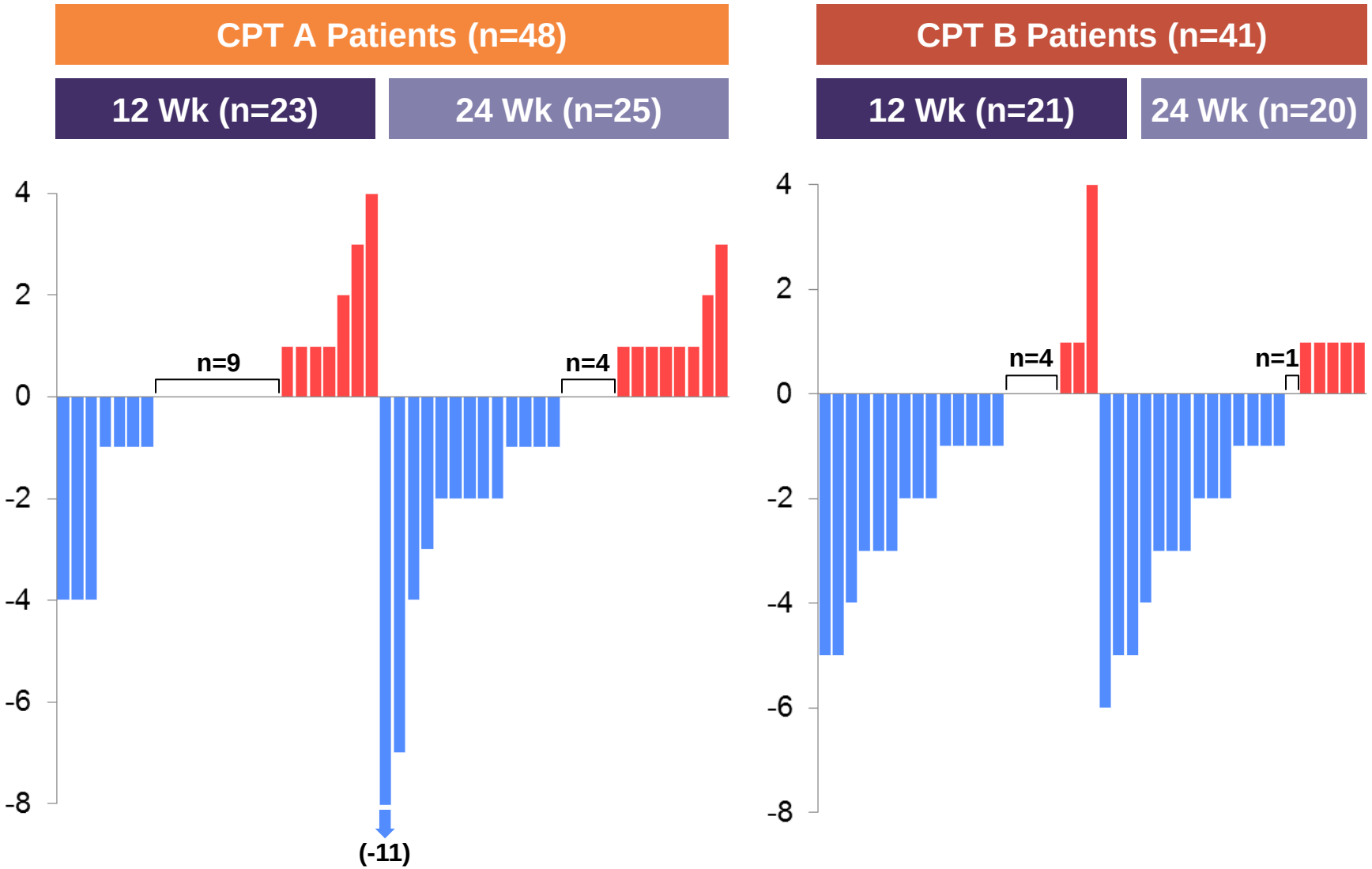
SOLAR-1. Change in MELD Score

Change From Baseline to Follow-Up Week 4



Missing FU-4: n=3 CPT A 12 wk; n=5 CPT B 12 wk; n=5 CPT B 24 wk

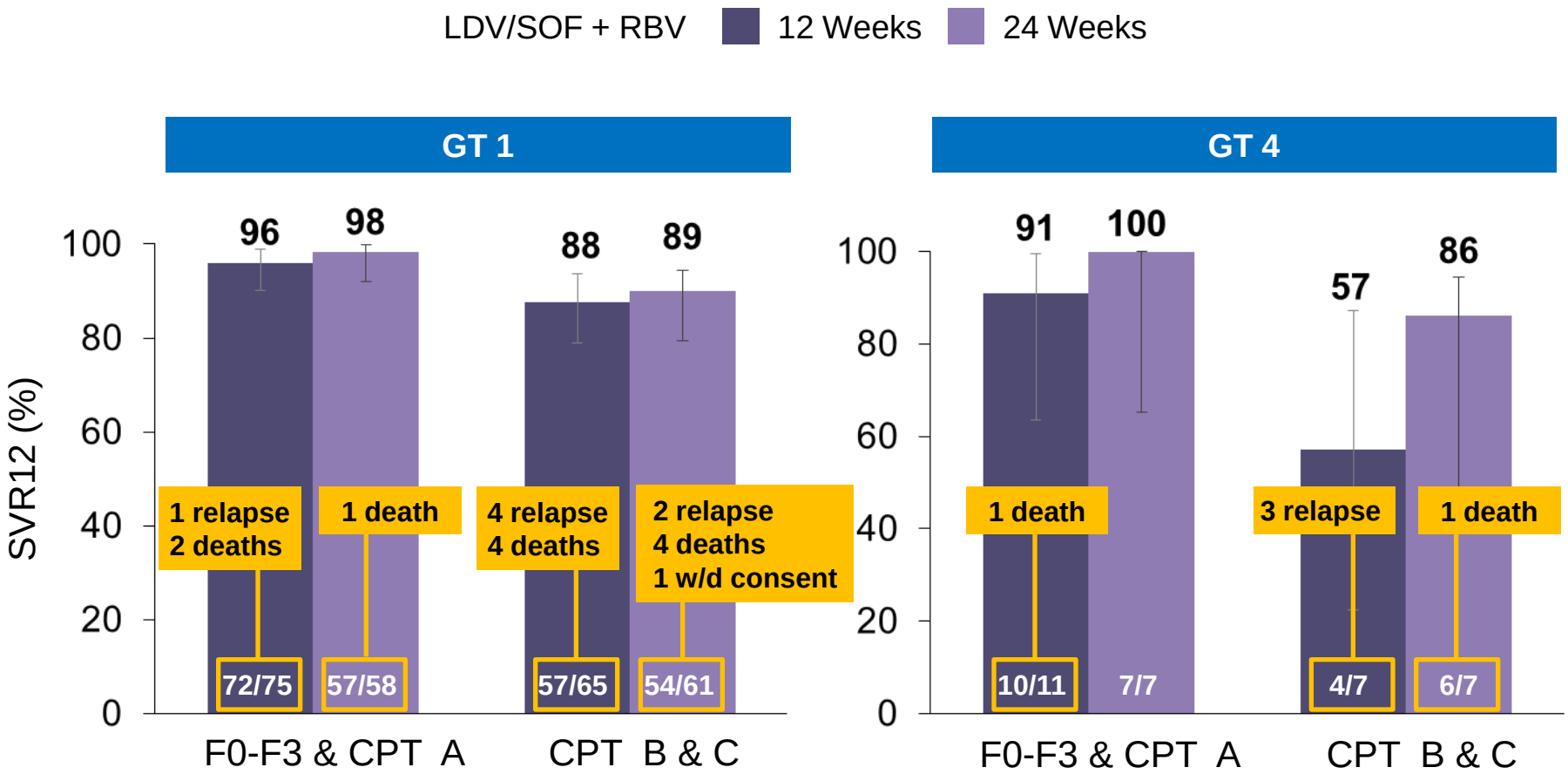
SOLAR-1: LDV/SOF + RBV in post-LT recurrence

Results: Overall Safety Summary

Subjects, n (%)	F0-F3		CTP A		CTP B		CTP C	
	12 Wk n=55	24 Wk n=56	12 Wk n=26	24 Wk n=25	12 Wk n=26	24 Wk n=26	12 Wk n=5	24 Wk n=4
AEs	55 (100)	55 (98)	25 (96)	24 (96)	25 (96)	26 (100)	5 (100)	4 (100)
Grade 3–4 AEs	15 (27)	14 (25)	4 (15)	7 (28)	6 (23)	9 (35)	1 (20)	1 (25)
Serious AEs	6 (11)	12 (21)	3 (12)	4 (16)	5 (19)	11 (42)	1 (20)	4 (100)
Serious and related AEs	2 (4)	1 (2)	2 (8)	2 (8)	0	1 (4)	0	0
Treatment DC due to AE	0	2 (4)	1 (4)	0	0	3 (12)	0	0
Treatment emergent death	0	0	1 (4)	0	1 (4)	2 (8)	0	0

SVR12 by Genotype

GT 1 and GT 4



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.

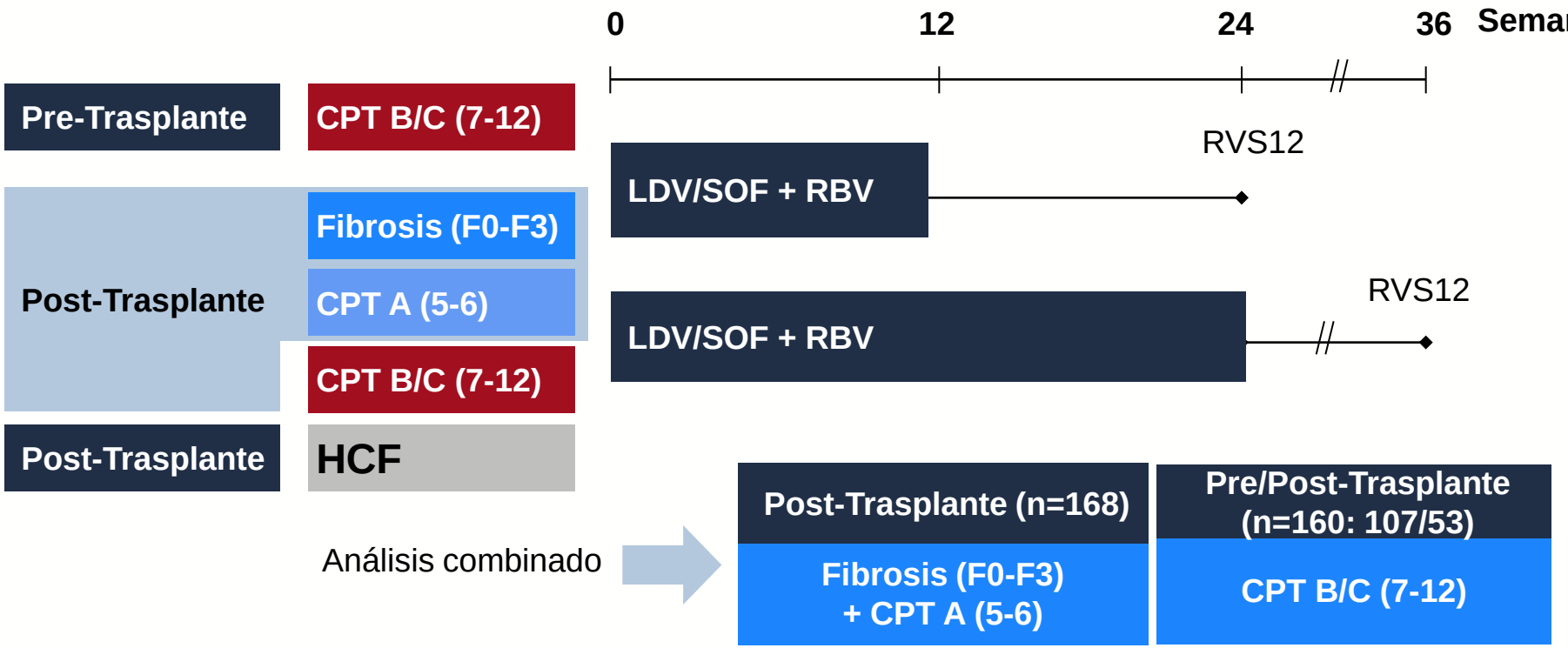
Ledipasvir/Sofosbuvir With Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients With HCV Infection: Preliminary Results of the SOLAR-2 Trial

Michael Manns[1], Xavier Forns[2], Didier Samuel[3], Jill Denning[4], Sarah Arterburn[4], Theo Brandt-Sarif[4], Hadas Dvory-Sobol[4], Phillip S. Pang[4], John G. McHutchison[4], Edward Gane[5], David Mutimer[6]

[1]Hannover Medical School, Hannover, Germany; [2]Liver Unit, IDIBAPS, CIBEREHD Hospital Clinic, Barcelona, Spain; [3]Université Paris-Sud, Villejuif, France; [4]Gilead Sciences, Foster City, California, USA; [5]University of Auckland, Auckland, New Zealand; [6]Queen Elizabeth Hospital and University of Birmingham, Birmingham, England

EASL 2015, Vienna

SOLAR-2: Ledipasvir (LDV)/Sofosbuvir (SOF) + RBV 12 o 24 sem en cirrosis descompensada y Hepatitis C post-TH GT 1 o 4 Estudio Fase II multicéntrico (n=329)



- 329 pacientes aleatorizados 1:1 a 12 o 24 semanas.
- GT 1 o 4 *naïve* o pretratados
- Criterios de exclusión: CPT 13-15, CL_{cr} < 40 mL/min, plaquetas < 30,000 x 10^3/µL.
- Dosis RBV: F0-F3 y CPT A ajustada a peso; CPT B-C 600-1200 mg/d

Manns M et al. EASL 2015. abstract GO2

SOLAR-2: LDV/SOF + RBV in Decompensated Cirrhosis

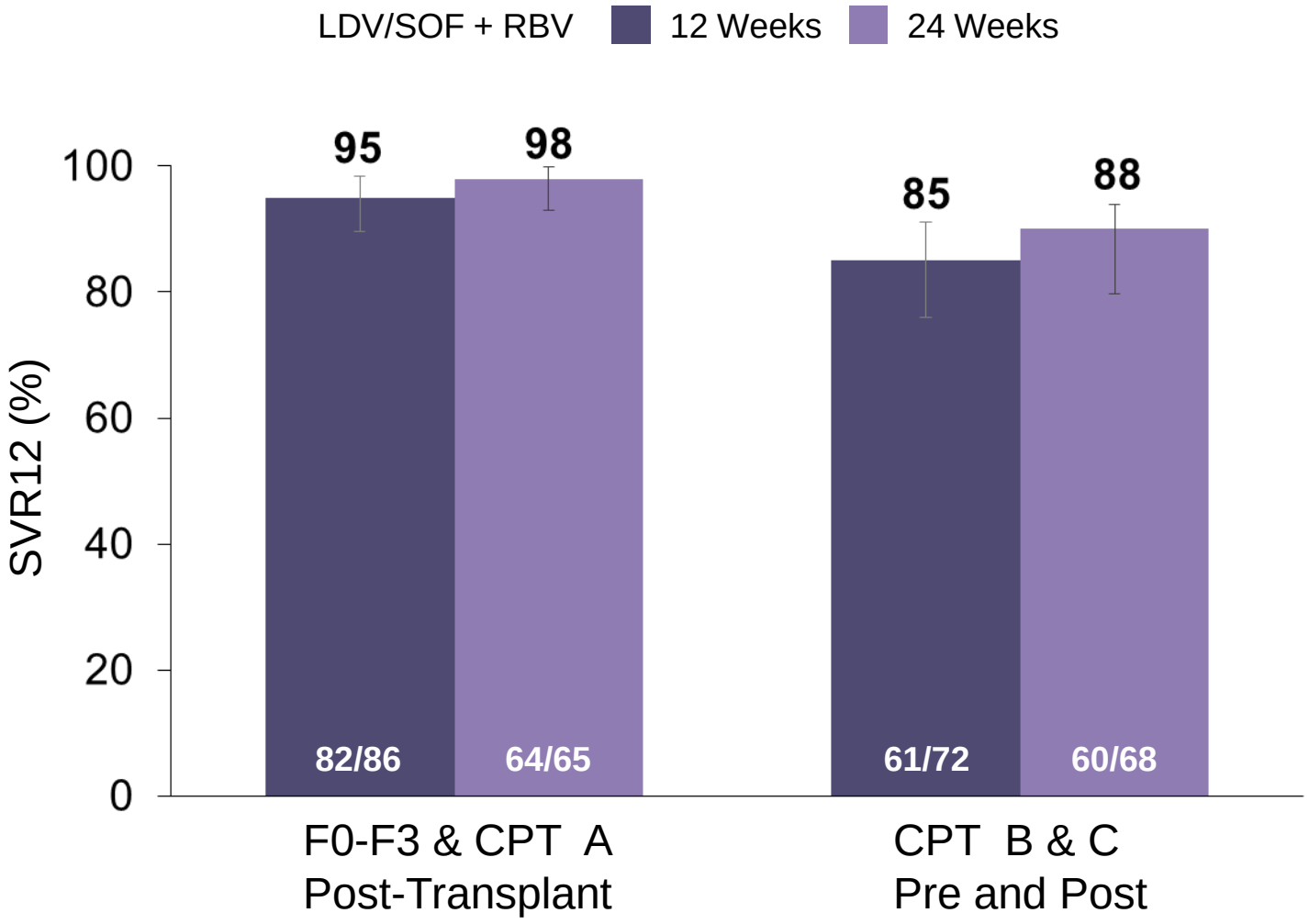
Demographics (n= 107)

	CTP B		CTP C	
	12 Weeks n=28	24 Weeks n=28	12 Weeks n=25	24 Weeks n=26
Median age, y (range)	57(52-61)	57 (52-62)	58 (53-63)	59 (47-62)
Male, n (%)	23 (82)	19 (68)	15 (60)	20 (77)
White, n (%)	25 (89)	28 (100)	23 (92)	25 (96)
Mean HCV RNA, log_{10} IU/mL (range)	6 ±0.5	5.9 ±0.6	5.6 ±0.6	5.7 ±0.4
GT 1a, n (%)	13 (46)	12 (43)	13 (52)	12 (46)
IL28B non-CC, n (%)	22 (79)	19 (68)	18 (72)	22 (85)
Prior HCV treatment, n (%)	25 (89)	24 (86)	13 (52)	18 (69)
MELD score, n (%)				
<10	2 (7)	6 (21)	2 (8)	0
10–15	22 (79)	18 (64)	11 (44)	15 (58)
16-20	4 (14)	4 (14)	10 (40)	9 (35)
21-25	0	0	2 (8)	2 (8)

Manns M et al, EASL 2015

Results: SVR12

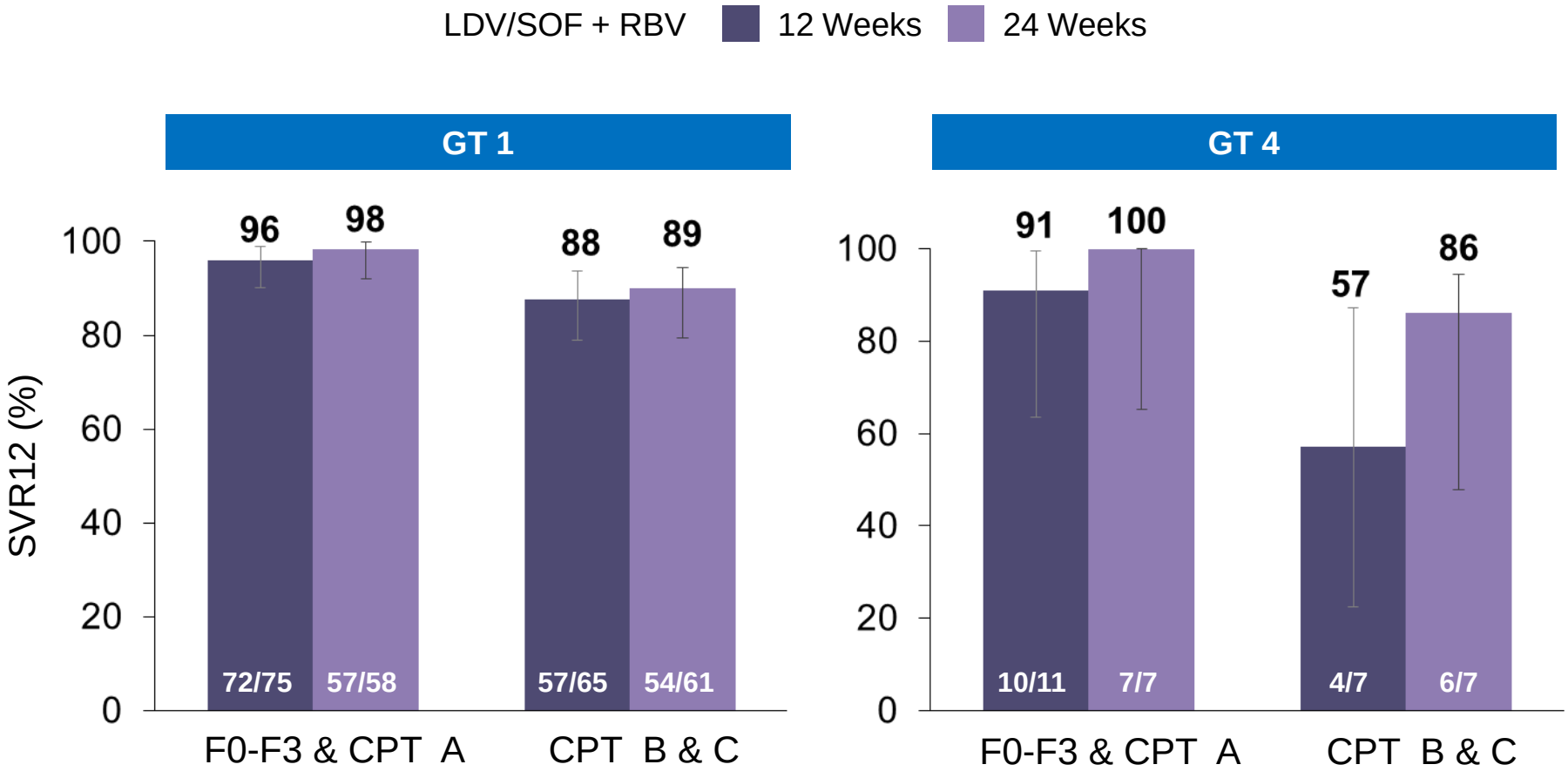
GS-US-334-0124



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.

SVR12 by Genotype

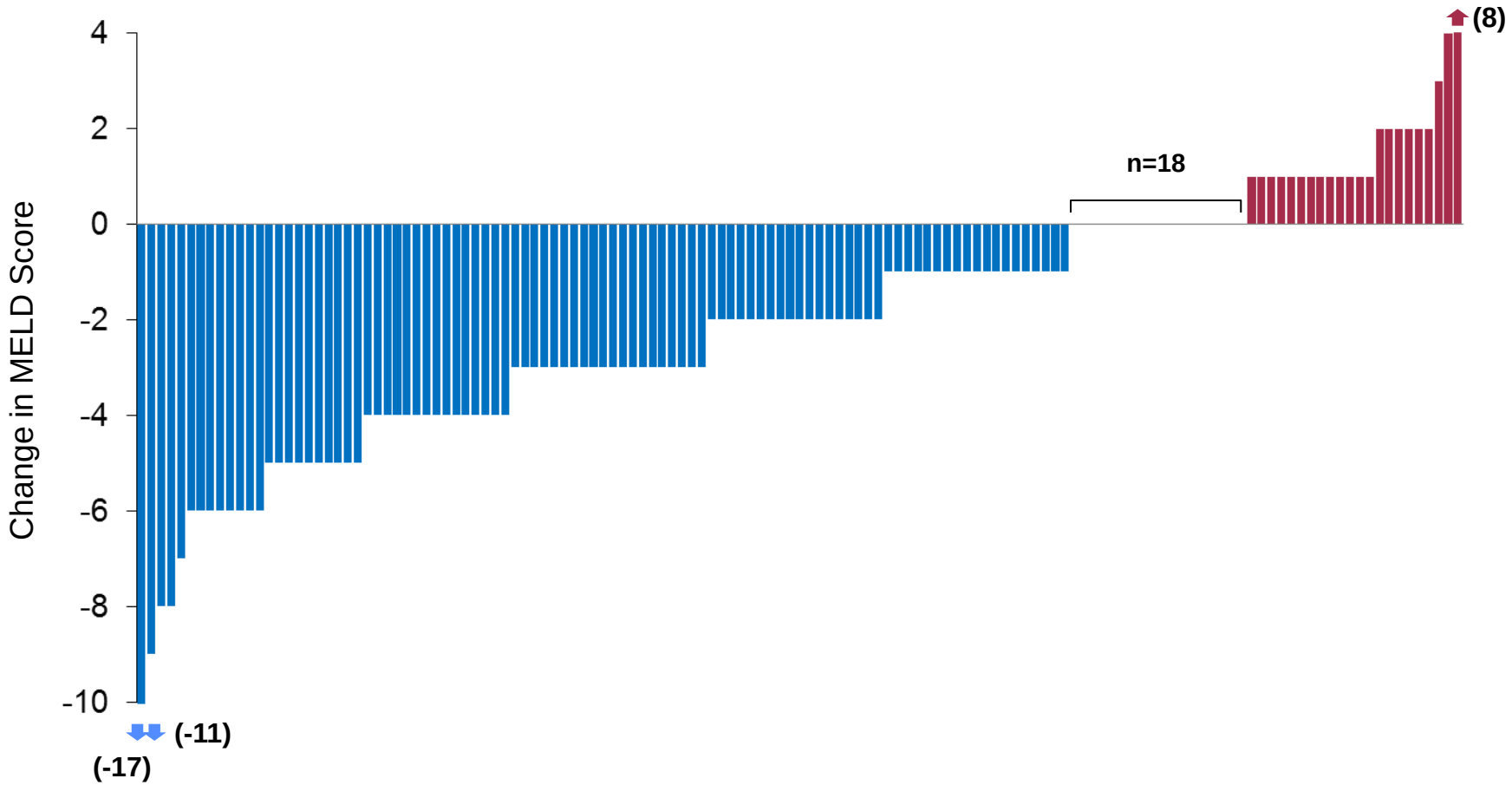
GT 1 and GT 4



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.

SOLAR-2: MELD Score Change From Baseline to Follow-up Week 4

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



*Missing FU-4: n=24.

SOLAR-2: Change in CPT Class From Baseline to Follow-up Week 4

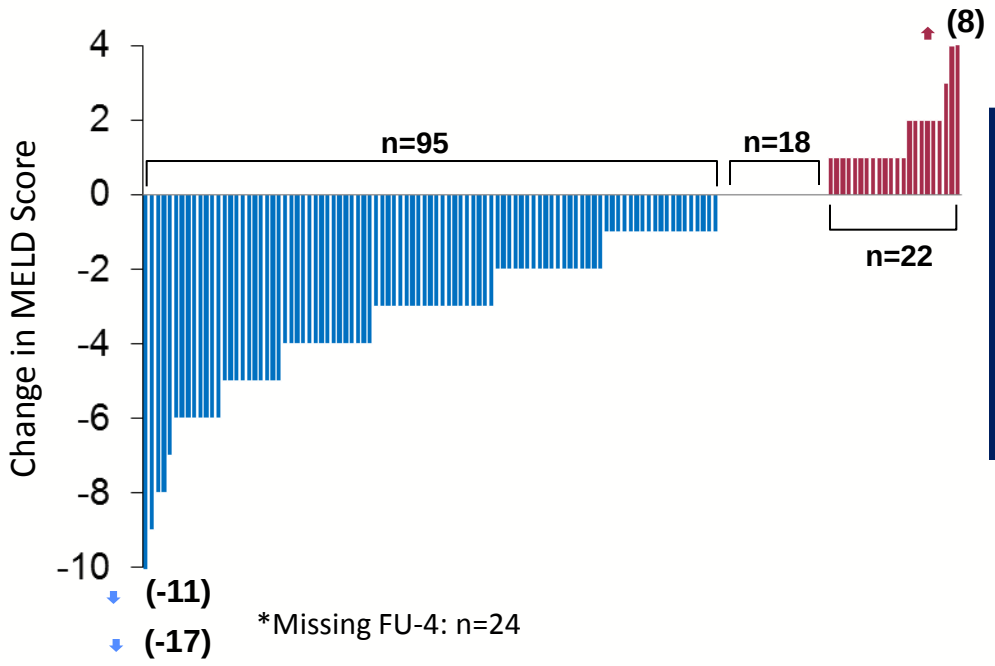
All Cirrhotic Subjects (CPT A, B, or C)

		Baseline CPT		
		A (5–6) n=73	B (7–9) n=100	C (10–12) n=54
Follow-up Week 4 CPT	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	3	12	12

SOLAR-2: Liver Function Change from Baseline to Follow-Up Week 4

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

Manns M et al. EASL 2015. abstract GO2

Baseline Demographics and Liver Disease Characteristics

	Pre-Transplant	Post-Transplant		
Patients, n (%)	**CTP B + C n=215**	**F0–3 + CTP A n=330**	**CTP B + C n=114**	**Total n=659**
HCV GT, n (%)				
1a	124 (58)	197 (60)	71 (62)	392 (59)
1b	78 (36)	111 (34)	36 (32)	225 (34)
4	13 (6)	22 (7)	7 (6)	42 (6)
IL28B non-CC, n (%)	167 (77)	272 (83)	92 (81)	431 (81)
Prior HCV treatment, n (%)	150 (70)	270 (82)	96 (84)	516 (78)
Cirrhosis, n (%)	215 (100)	118 (36)	114 (100)	447 (68)
Median eGFR, mL/min/1.73 m^2 (range)	84 (34–224)	63 (20–132)	64 (29–124)	69 (20–224)
MELD, n (%)				
<10	24 (11)	64 (54)	26 (23)	114 (26)
10-15	132 (61)	51 (43)	69 (61)	252 (56)
16–20	54 (25)	3 (3)	16 (14)	73 (16)
21–25	5 (2)	0	3 (3)	8 (2)
Median albumin, g/dL (range)	2.8 (1.6–4.0)	3.9 (2.4–4.8)	3.0 (1.6–4.2)	NR
Median platelets, x 10^3/µL (range)	76 (27–212)	136 (35–434)	90 (32–237)	NR
Ascites, n (%)	163 (76)	9 (3)	83 (73)	NR
Encephalopathy, n (%)	140 (65)	4 (1)	53 (46)	NR

NR, not reported
Samuel, EASL, 2015, P0774

SOLAR-2. HUP La Fe

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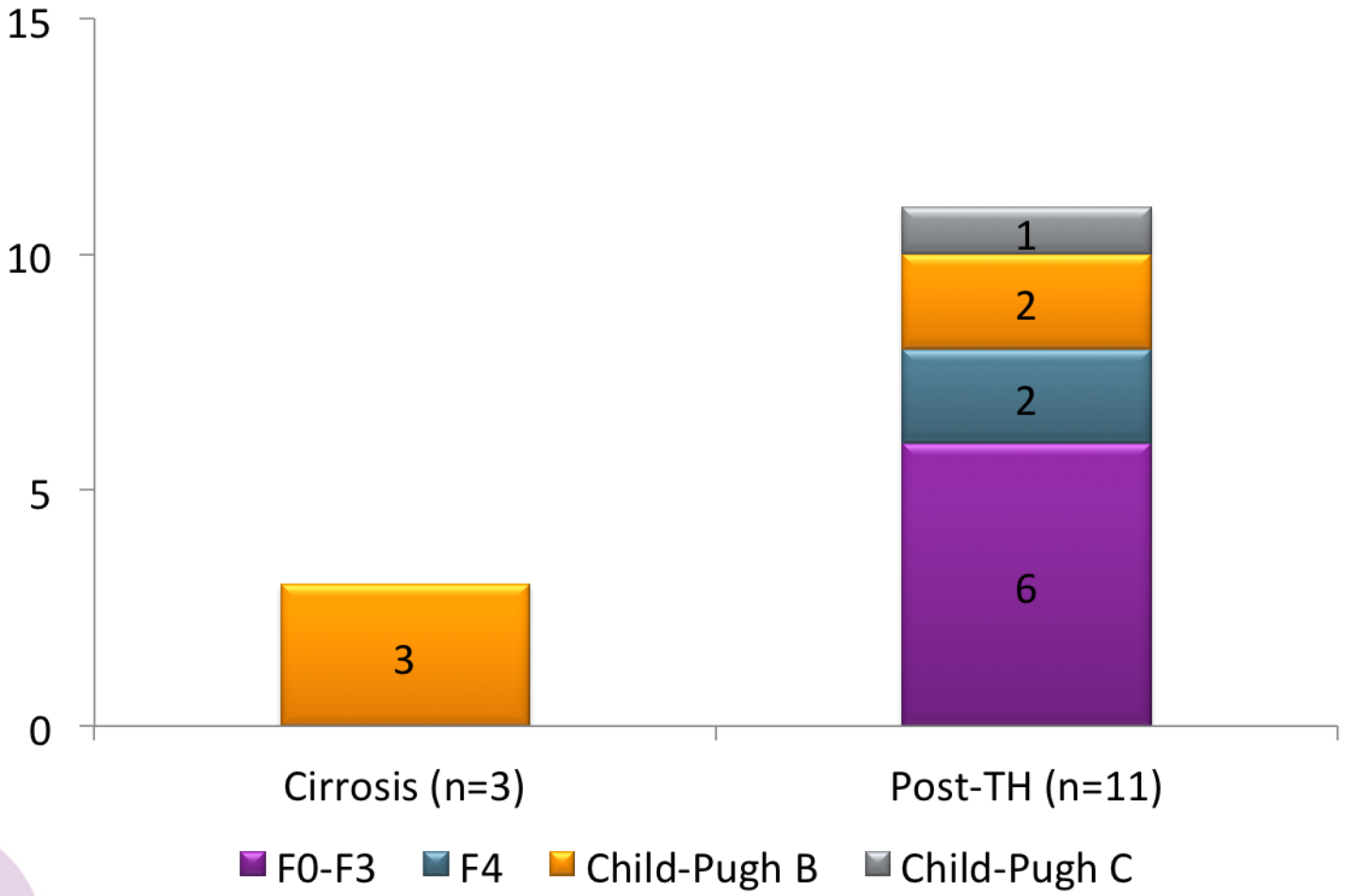
SOLAR-2. HUP La Fe. Población de estudio (n=14)

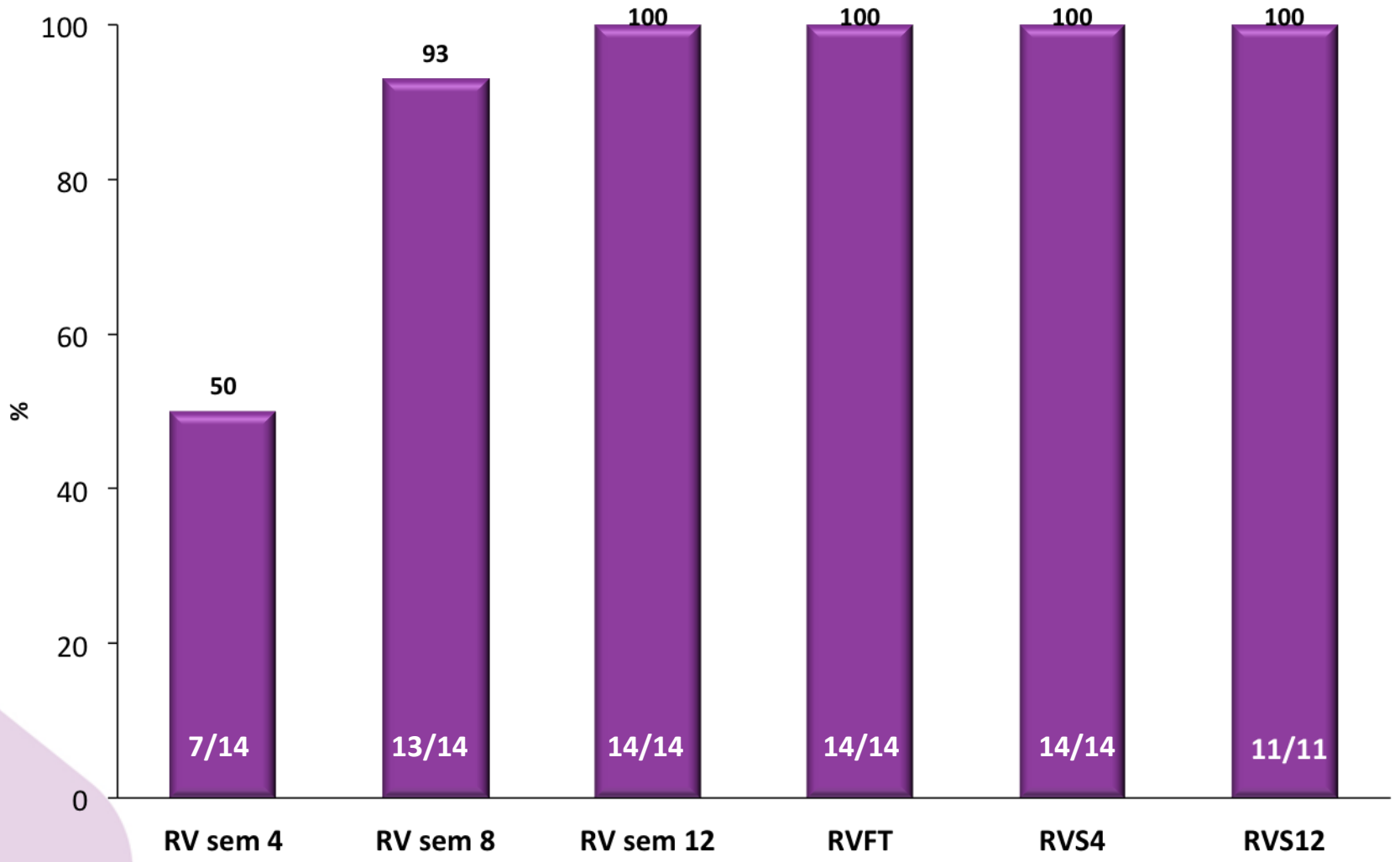


SOLAR-2. HUP La Fe. Características demográficas

	n=14
Edad (años), mediana (rango)	62 (43-75)
Hombres, n (%)	11 (79)
IMC ≥30, n (%)	6 (43)
Genotipo 1, n (%)	13 (93)
IL28 no CC, n (%)	10 (71)
Tratº previo, n(%)	8 (57)
ARN VHC log UI/mL , mediana (rango)	6,5 (3,4-8,3)
MELD, mediana (rango)*	12 (7-19)
Ascitis, n (%)*	2 (25)
Encefalopatía*, n (%)	1 (12)
Tº desde el TH (años), mediana (rango)**	10,4 (1,4-17)
Duración 12/24 sem, n	5/9

*sólo en cirrosis pre/post-TH (n=8), **sólo en post-TH (n=11)

SOLAR-2. HUP La Fe. Respuesta virológica global (ITT)



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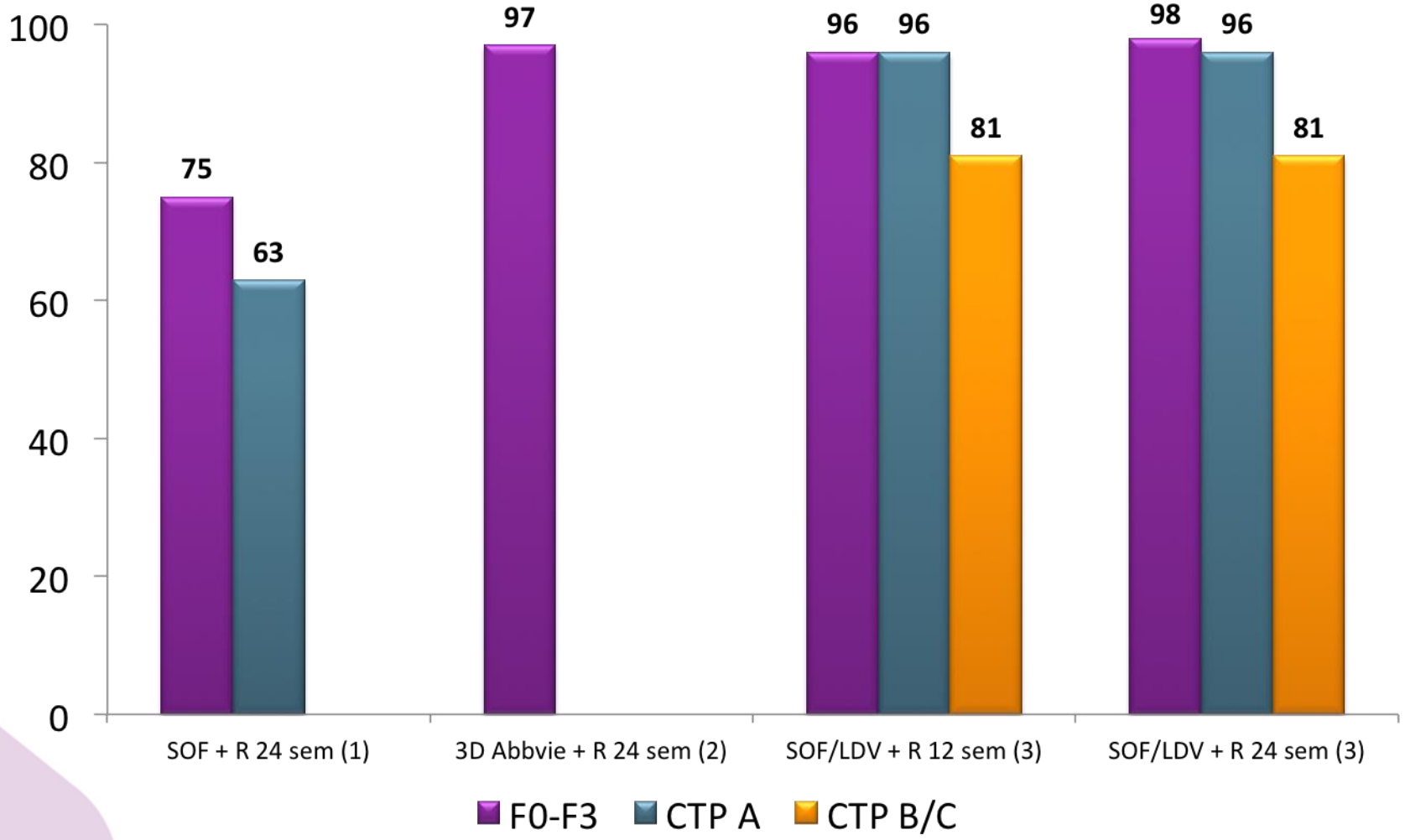
Regímenes libres de IFN en Hepatitis C post-TH



(1) Charlton M. Gastro 2015; (2) Kwo PY. NEJM 2014; (3) Reddy KR. AASLD 2014

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Recomendaciones GPC EASL y AASLD en Hep C recurrente

No cirrosis y cirrosis compensada

Genotipo	EASL (1)	AASLD-IDSA (2)
G 1	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem SOF + SIM + RBV 12 sem 3D + RBV 12 sem (1b) o 24 sem (1a con cirrosis)	**SOF/LDV + RBV 12 sem** SOF/LDV 24 sem (intol/ineleg RBV) SOF + SIM + RBV 12 sem 3D + RBV 24 sem (F0-F2)
G 2	SOF + RBV 12 sem SOF + DCV + RBV 12 sem	**SOF + RBV 24 sem**
G 3	SOF + DCV + RBV 12 sem	**SOF + RBV 24 sem**
G 4	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem SOF + SIM + RBV 12 sem 2D + RBV 12 sem (sin cirrosis) o 24 sem (cirrosis)	**SOF/LDV + RBV 12 sem** SOF/LDV 24 sem (intol/ineleg RBV)
G 5/6	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem	-

(1) EASL Recommendations on treatment of hepatitis C 2015. April 2015

(2) AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. accessed 9 may 2015

Recomendaciones GPC EASL y AASLD en Hep C recurrente

Cirrosis descompensada

Genotipo	EASL (1)	AASLD-IDSA (2)
G 1	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem	**SOF/LDV + RBV 12 sem** SOF/LDV 24 sem (intol/ineleg RBV)
G 2	SOF + RBV 12 sem SOF + DCV + RBV 12 sem	**SOF + RBV 24 sem**
G 3	SOF + DCV + RBV 12 sem	**SOF + RBV 24 sem**
G 4	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem	**SOF/LDV + RBV 12 sem** SOF/LDV 24 sem (intol/ineleg RBV)
G 5/6	SOF/LDV + RBV 12 sem SOF + DCV + RBV 12 sem	-

(1) EASL Recommendations on treatment of hepatitis C 2015. April 2015

(2) AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. accessed 9 may 2015