ALCANZAR LA RVS AHORA PUEDE SER SIMPLE: EXPERIENCIA EN VIDA REAL

Eficàcia en pacients tractats 8 setmanes Dades en vida real

Dr Xavier Xiol

Hospital Universitari de Bellvitge

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 15, 2014 VOL. 370 NO. 20

Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

Kris V. Kowdley, M.D., Stuart C. Gordon, M.D., K. Rajender Reddy, M.D., Lorenzo Rossaro, M.D., David E. Bernstein, M.D., Eric Lawitz, M.D., Mitchell L. Shiffman, M.D., Eugene Schiff, M.D., Reem Ghalib, M.D., Michael Ryan, M.D., Vinod Rustgi, M.D., Mario Chojkier, M.D., Robert Herring, M.D., Adrian M. Di Bisceglie, M.D., Paul J. Pockros, M.D., G. Mani Subramanian, M.D., Ph.D., Di An, Ph.D., Evguenia Svarovskaia, Ph.D., Robert H. Hyland, D.Phil., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., David Pound, M.D., and Michael W. Fried, M.D., for the ION-3 Investigators*

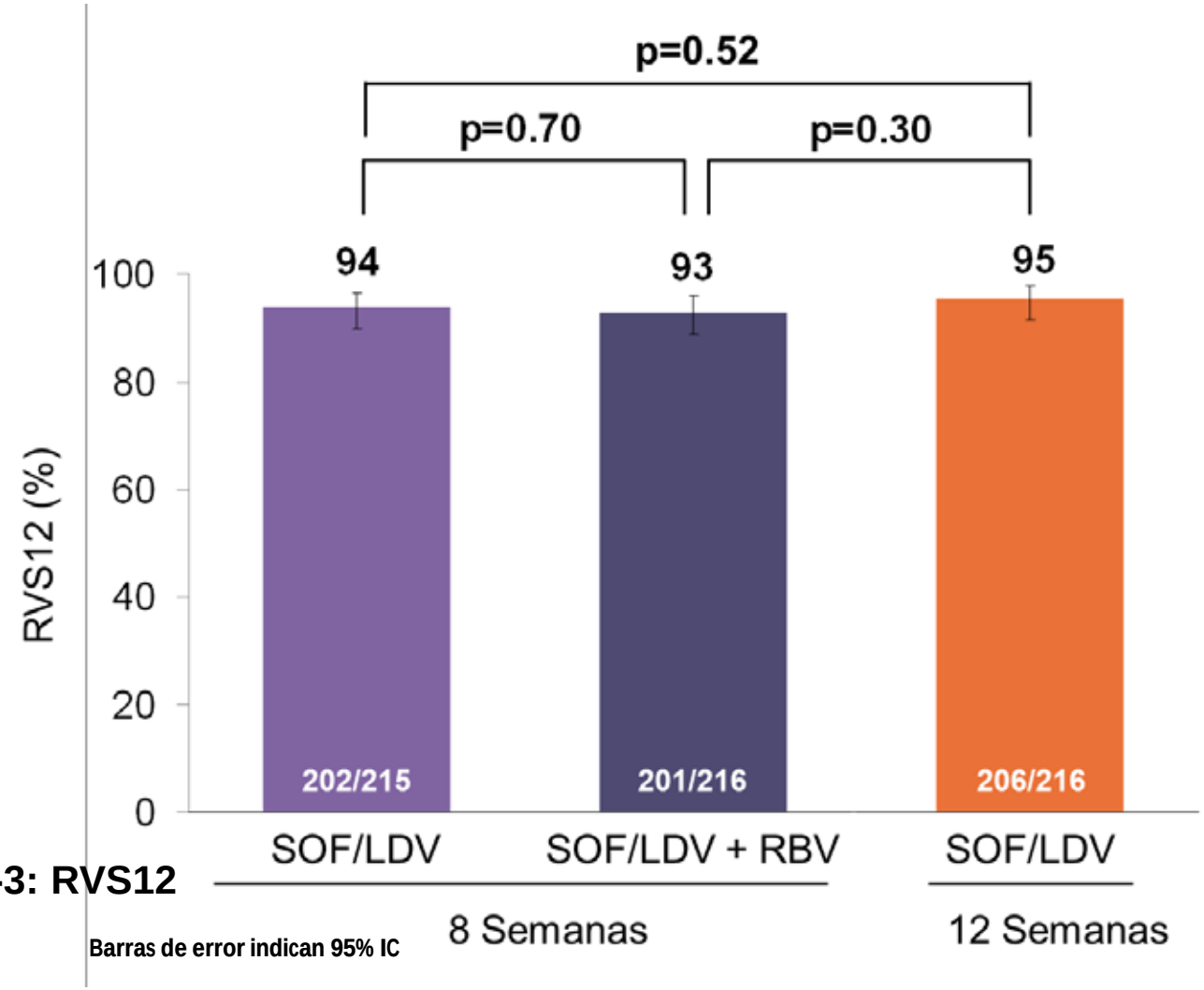
In this phase 3, open-label study, we randomly assigned 647 previously untreated patients with HCV genotype 1 infection without cirrhosis to receive ledipasvir and sofosbuvir (ledipasvir–sofosbuvir) for 8 weeks, ledipasvir–sofosbuvir plus ribavirin for 8 weeks, or ledipasvir–sofosbuvir for 12 weeks. The primary end point was sustained virologic response at 12 weeks after the end of therapy.

LDV/SOF ± RBV pacients VHC genotip 1 sense cirrosi (F0-F3) i sense tractament previ (ION-3)

Caracteristica	8 setmanes		12 setmanes
	LDV/SOF *n* = 215	LDV/SOF+RBV *n* = 216	LDV/SOF *n* = 216
Edat mitja, anys	53 (22-75)	51 (21-71)	53 (20-71)
Homes, *n* (%)	130 (61)	117 (54)	128 (59)
Raça negra, *n* (%)	45 (21)	36 (17)	42 (19)
Hispans, *n* (%)	13(6)	12(6)	14(7)
Fibrosi score F0-F2 F3	156 127 29	136 108 28	156 127 29
IL28B CC, *n (%)*	56 (26)	60 (28)	56 (26)
Genotip 1a, *n* (%)	171 (80)	172 (80)	172 (80)
ARN mig basal, log_{10} U	6,5 ± 0,76	6,4 ± 0,69	6,4 ± 0,76
ARN VHC ≥ 800.000 , *n* (%)	181 (84)	171 (79)	172 (80)

1. Kowdley KV, et al. 49th EASL 2014 Oral #56. Kowdley KV, et al. N Engl J Med. 2014;370:1879-1888.

ION 3: Resposta viral sostinguda

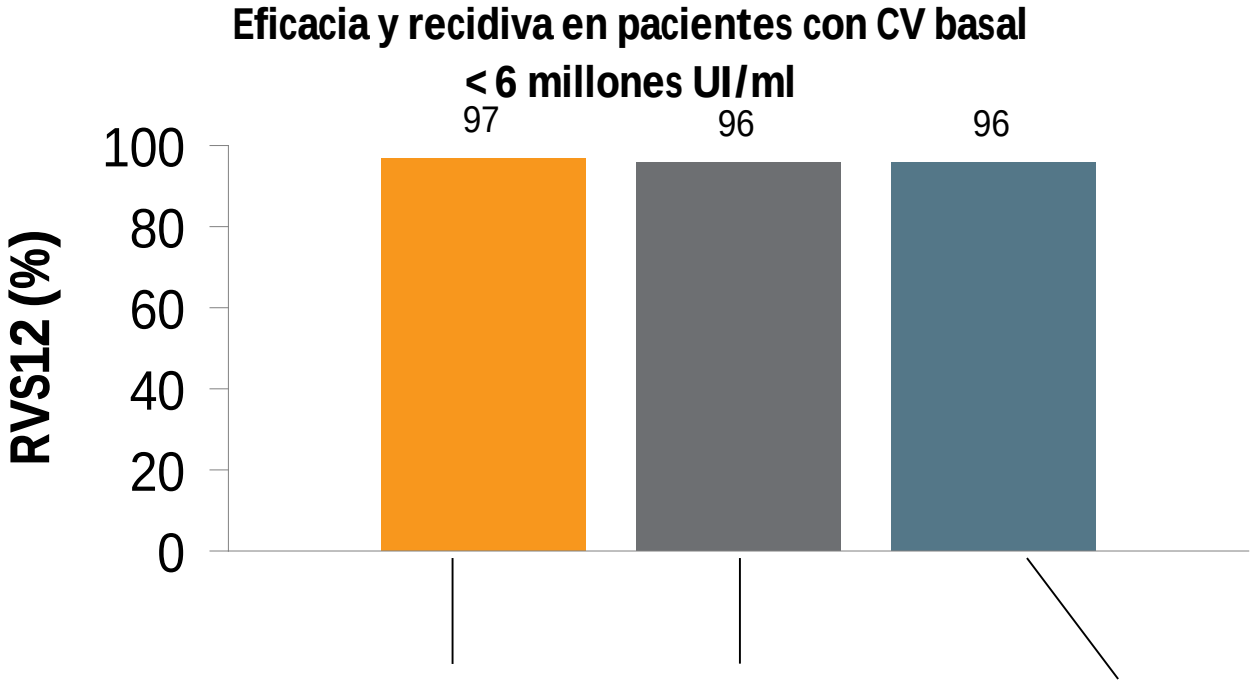


ION-3: RVS12

Barras de error indican 95% IC

Kowdley KV, et al. 49th EASL 2014 Oral #56. Kowdley KV, et al. N Engl J Med. 2014;370:1879-1888.

Sofosbuvir + Ledipasvir. ION 3



	LDV/SOF 8 setmanes	*LDV/SOF + RBV 8 setmanes	LDV/SOF 12 setmanes
Taxa recaigudes < 6M	1,6% (2/123)	2,2% (3/137)	1,5% (2/131)
Taxa recaigudes ≥ 6M	9,8% (9/92)	7,8% (6/77)	1,2% (1/85)

Wyles D. TUPEB249 IAS 2015

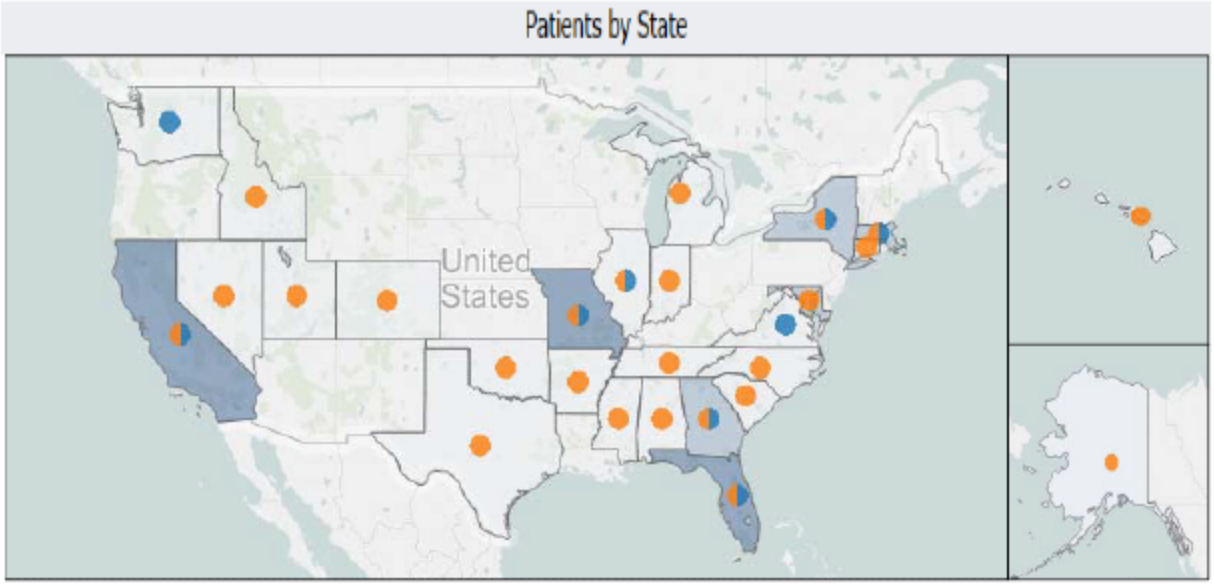
Dades en vida real

- No articles publicats

- Abstracts Congressos AASLD 2015

Trio Real-World Cohort

Patients by Site Type



	LDV-SOF 8 week	LDV-SOF +/- RBV* 12 week	Grand Total
Academic: n (%)	86 (32%)	256 (41%)	342 (38%)
Community: n (%)	177 (67%)	376 (59%)	553 (62%)
Total:	263	632	895

*21 Patients were on 12 weeks of LDV-SOF+RBV

Data source: Trio Health

TRIO Real-World Cohort

LDV/SOF ± RBV for 8 or 12 Weeks in Treatment-Naïve, Non-Cirrhotic GT 1 HCV

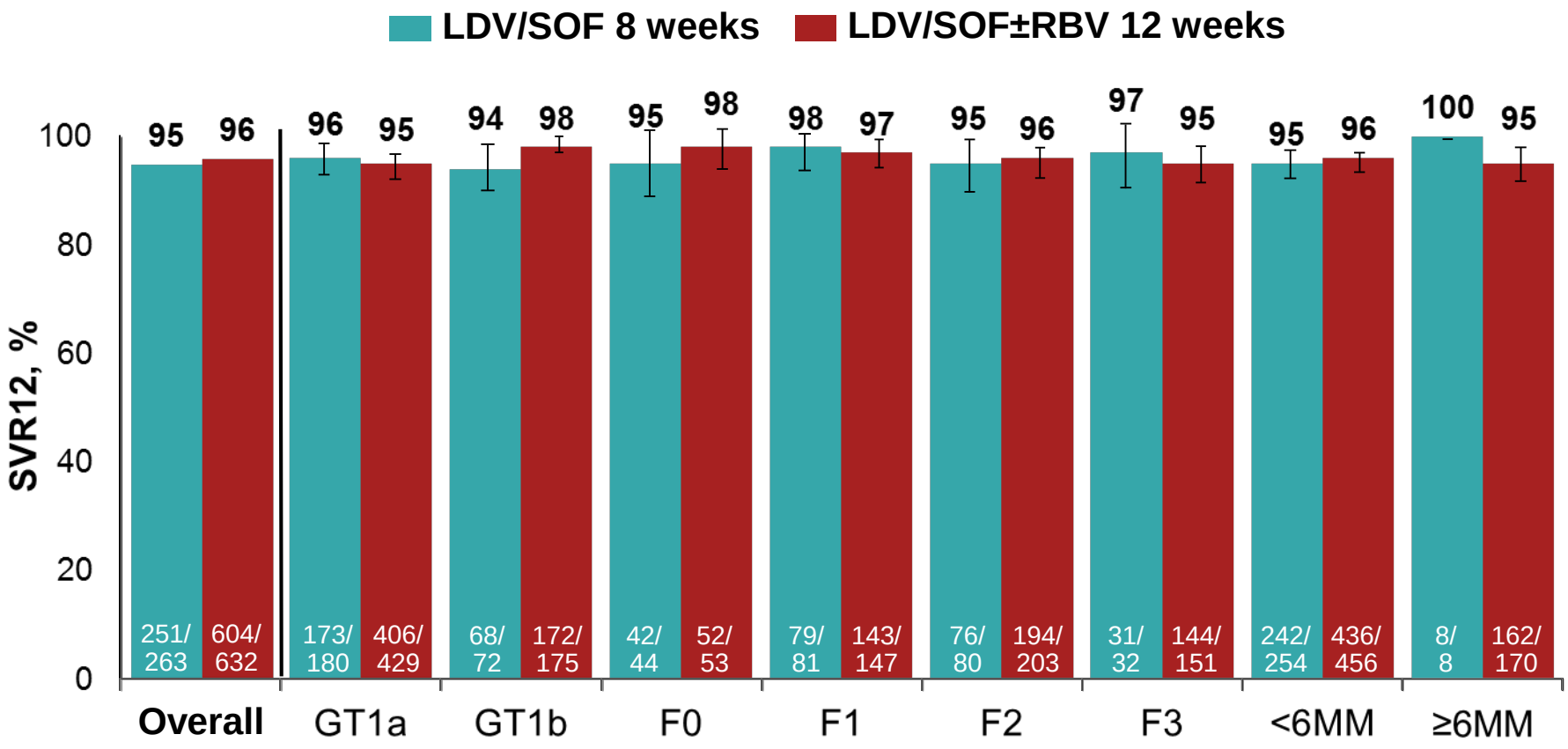
Real-world observational study of 895 patients treated with LDV/SOF±RBV for 8 or 12 weeks at academic (38%) and community medical centers (62%) in the US

	LDV/SOF 8 Week n=263	LDV/SOF±RBV 12 Week n=632
Academic practice, n (%)	86 (32)	256 (41)
Age, mean (range)	57 (18–84)	60 (19–89)
Male, n (%)	121 (46%)	353 (56%)
Patient Ethnicity, n (%)		
Black	39 (15%)	118 (19%)
White	152 (58%)	306 (48%)
Severe Fibrosis (F3), n (%)	**32 (12%)**	**151 (24%)**
Genotype, n (%)		
1a	**180 (68%)**	**429 (68%)**
1b	**72 (27%)**	**175 (27%)**
Initial Viral Load, n (%)		
<6MM IU/ml	**254 (97%)**	**456 (72%)**
≥6MM IU/ml	**8 (3%)**	**170 (27%)**
Unknown	**1 (<1%)**	**6 (1%)**

Curry, AASLD, 2015, 1046

Overall SVR12 and by Subgroup (ITT Analysis)

Overall discontinuation rate was <1% (7/895)



ITT analysis.
Curry, AASLD, 2015, 1046

HCV-TARGET Real-World Cohort

Treatment Outcomes with LDV/SOF for 8, 12 & 24 Weeks

HCV- TARGET is a consortium of academic (n=44) and community medical centers (n=17) in North America (n=47) and Europe (n=4) conducting a longitudinal, observational study of HCV treatment

Terrault, AASLD, 2015, 94

Treatment Outcomes with LDV/SOF for 8, 12 & 24 Weeks

Analysis of 1,270 patients who received LDV/SOF±RBV in HCV-TARGET, a multicenter, prospective, observational, real-world cohort study

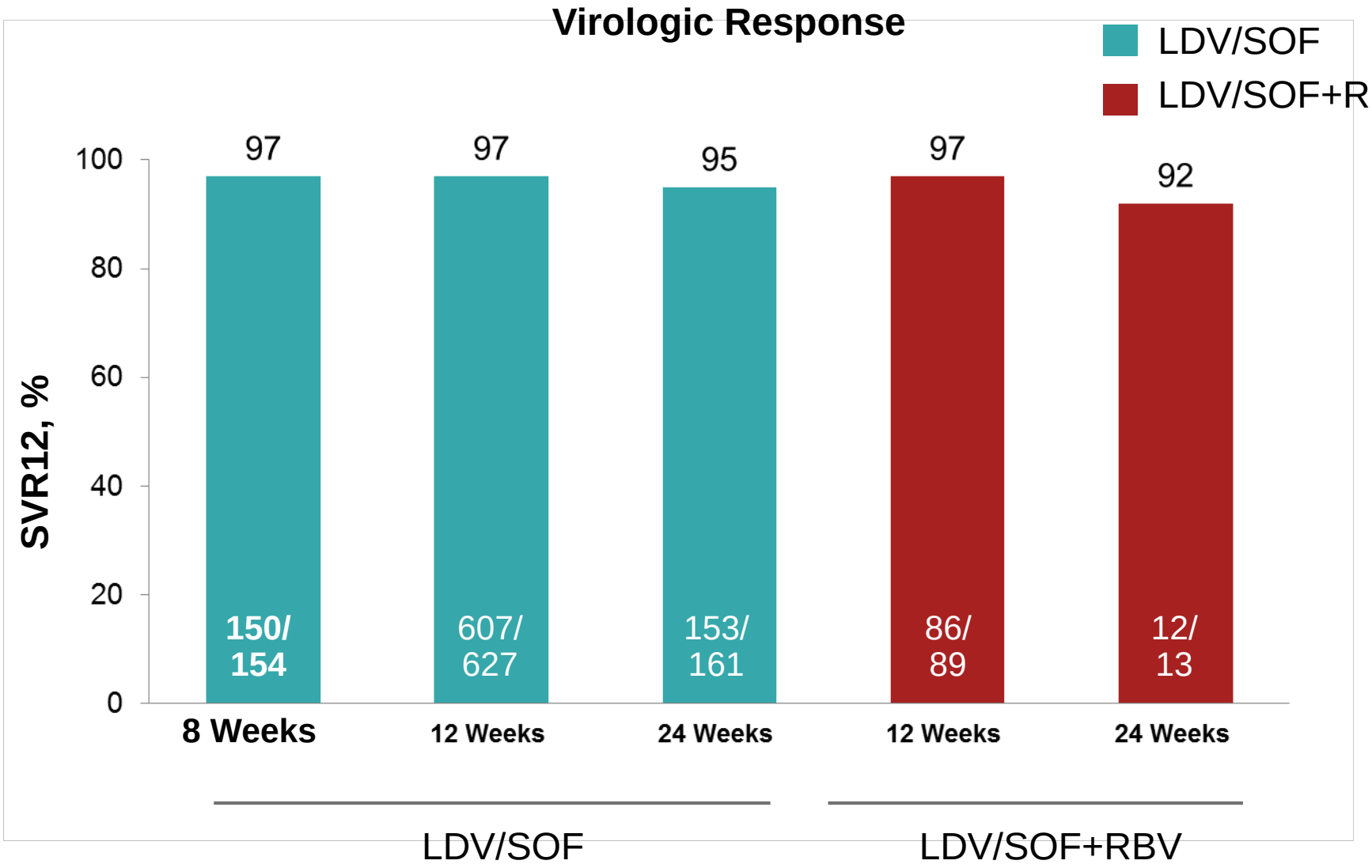
	LDV/SOF N=1139	LDV/SOF+RBV N=131
Male, n (%)	647 (57)	90 (69)
Age, yr, median, range	60 (19-87)	61 (31-78)
Caucasian, n (%)	814 (72)	108 (82)
Black, n (%)	245 (22)	12 (9)
Treatment Status, n (%)		
Naïve	634 (56)	40 (31)
Experienced	505 (44)	91 (69)
DAA Experienced	143 (13)	24 (18)
Genotype, n (%)		
1a	751 (66)	79 (60)
1b	302 (27)	40 (31)
Cirrhosis, n (%)	396 (35)	83 (63)
Decompensated, n (%)	142 (13)	28 (21)
Liver transplant, n (%)	71 (6)	58 (44)
HIV, n (%)	35 (3)	4 (3)
Baseline PPI Use, n (%)	305 (27)	47 (36)

Terrault, AASLD, 2015, 94

Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF. Proton pump inhibitors should not be taken before LDV/SOF. (Harvoni® SmPC)

HCV-TARGET Real-World Cohort

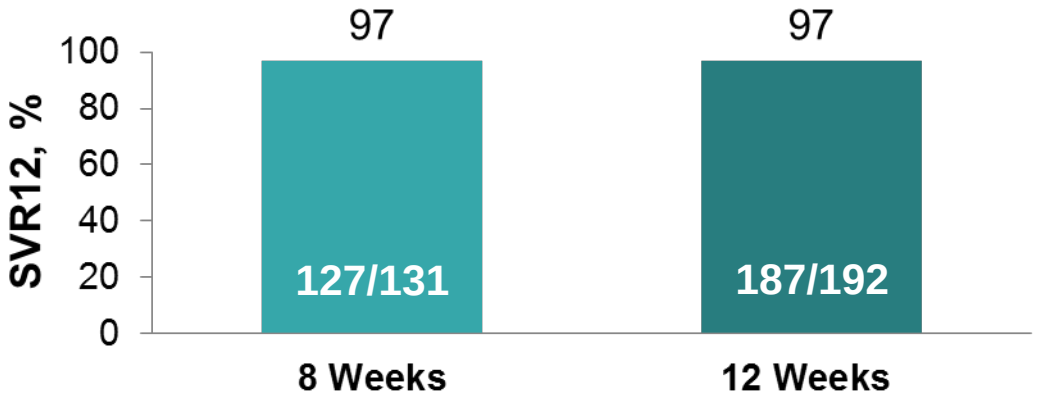
SVR12 Results with LDV/SOF±RBV for 8, 12, and 24 Weeks (Per Protocol Analysis)



Terrault, AASLD, 2015, 94

SVR12 Among Those Who Qualified for 8 Week Treatment

323 Qualified for 8 Weeks Therapy*



*Qualified = Treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL

99/131 had available Week 4 HCV RNA

HCV4 BLOQ N=92	HCV4 QUANT N=7 (8%)
SVR = 89 Relapse = 3	SVR = 7 Relapse = 0

133/192 had available Week 4 HCV RNA

HCV4 BLOQ N=117	HCV4 QUANT N=16 (12%)
SVR = 114 Relapse = 3	SVR = 15 Relapse = 1

No role for response-guided therapy was identified

Terrault, AASLD, 2015, 94

HCV-TARGET Real-World Cohort: Treatment Outcomes with LDV/SOF for 8, 12, and 24 Weeks

Safety (AEs > 10%)

	LDV/SOF N=1435	LDV/SOF + RBV N=213
Any AE, n (%)	900 (63)	178 (84)
Fatigue	320 (22)	75 (35)
Headache	307 (21)	50 (24)
Anaemia	8 (1)	53 (25)
Nausea	109 (8)	25 (12)
Diarrhoea	86 (6)	22 (10)
Rash	30 (2)	21 (10)
Pruritus	27 (2)	21 (10)

Terrault, AASLD, 2015, 94

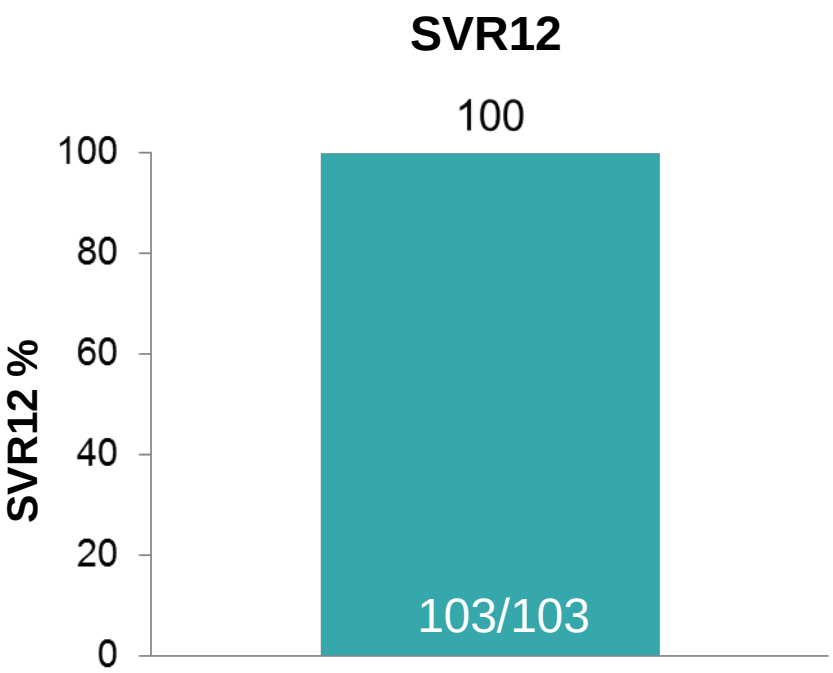
German Real-World LDV/SOF for 8 Weeks

Single center German study of 103 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks

Christensen, AASLD, 2015, 1081

German Real-World LDV/SOF for 8 Weeks

	N=103
Median (range) age, years	50 (22–77)
Male gender, n (%)	43 (42)
Caucasian, n (%)	103 (100)
Genotype, n (%)	
GT 1a	49 (46)
GT 1b	52 (51)
GT 4	2 (2)
Metavir stage, n (%)	
F0	56 (54)
F1	25 (24)
F2	17 (17)
F3	5 (5)
Median baseline HCV RNA, IU/mL*	870,964
Treatment-naïve, n (%)†	100 (97)
HIV/HCV coinfection, n (%)	3 (3)
At least one comorbidity, n (%)	94 (91)



LDV/SOF for 8 weeks resulted in high rates of SVR12 and was well tolerated

- 2.3% (n=2) had Grade 3 or 4 AEs
- No AE led to treatment discontinuation or death

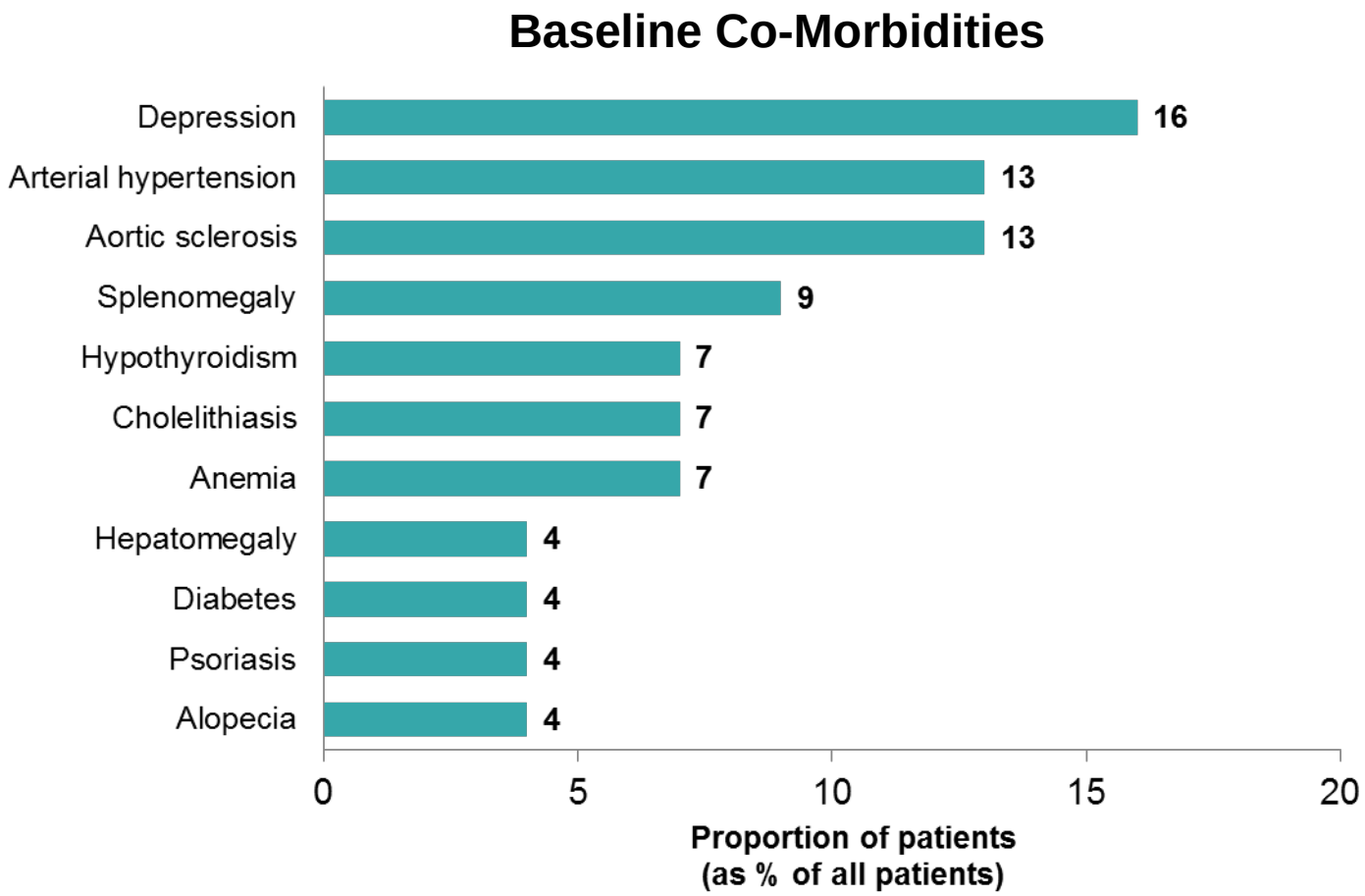
*Roche COBAS® AmpliPrep/COBAS® TaqMan®, cut-off < 12 IU/mL † including 3 PegIFN+RBV Relapsers
Fibrosis was measured by FibroScan® with cut-off values for METAVIR stage F3 or less of ≤12.3kPa.

Buggisch, AASLD, 2015, 1205.

German Real-World LDV/SOF for 8 weeks in NC with HCV RNA < 6M, primarily TN GT 1

Baseline Co-Morbidities

Single center German study of 45 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks



Buggisch, EASL, 2015, LP32

GECCO: German cohort

Baseline characteristics – SL8

	Overall (n=148)
Male sex, n(%)	72 (49)
Median age [years] (IQR)	52 (44-58)
Transmission IVDU/MSM/blood, n(%)	46(31)/15(10)/ 36(24)
HCV genotype 1/4, n(%)	144(97)/3(2)
Median HCV viral load [IU/mL] (IQR)	$8.1x10^5$ ($2.5x10^5$-$1.7x10^6$)
Median ALT [U/L] (IQR)	56 (37-89)
Prior HCV treatment, n (%)	26 (18)
Fibroscan >12.5kPa or APRI >2, n(%)	5 (3)
HIV coinfection, n (%)	28 (19)
Median CD4 cell count [/mm^3] (IQR)	531 (346-683)

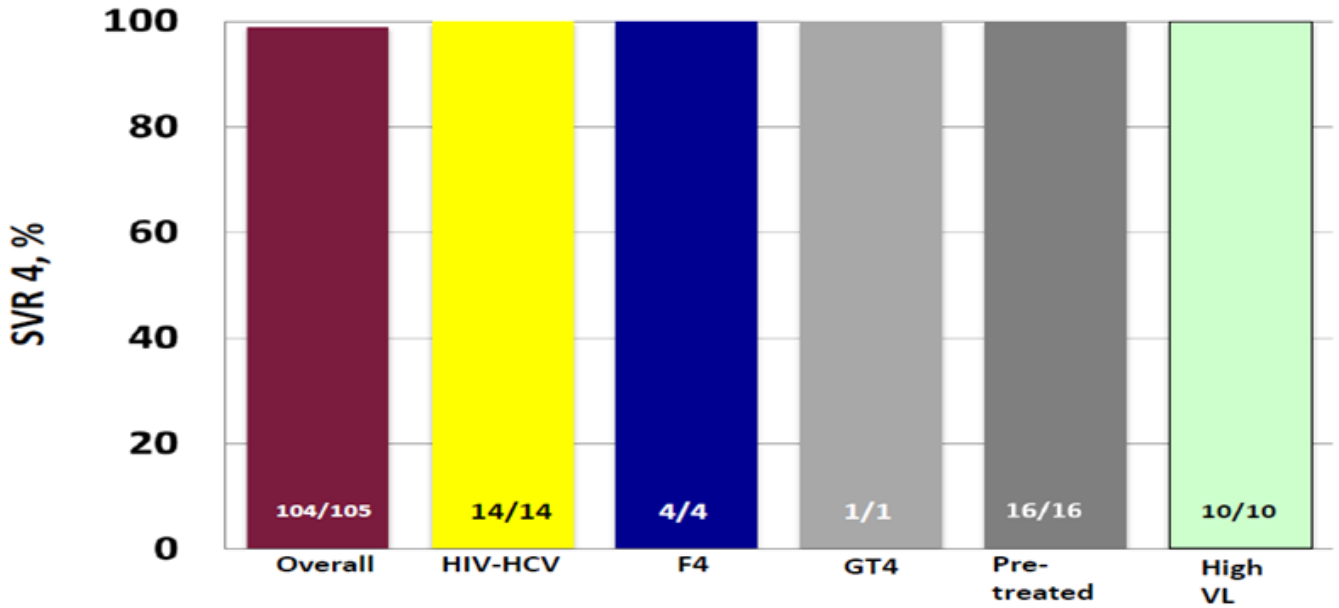
Bonn, Berlin, Dusseldorf, Frankfurt, Leverkusen,Hamburg, Muenster

Christensen, AASLD, 2015, 1081

GECCO: German cohort

Efficacy SL8

- Sofosbuvir-ledipasvir for 8 weeks in real-life, SVR 4: 99%



Metavir F4 defined as APRI > 2 OR Fibroscan > 12.5kPa, high VL load defined as > 2mio IU/ml (Abbott PCR) or 6 mio IU/ml (Roche PCR), prior treatment was interferon-based (in one case with sofosbuvir)
SVR, sustained virological response; APRI, AST-to-platelets ratio index; NR, nonresponder; R, relapser; VL, viral load

Cohort Alemanya. Pràctica clínica

Christensen, AASLD, 2015, 1081

Experiència pròpia

Referència: WJS232061088

135

Tractament de l'hepatitis crònica C genotip 1 amb sofosbuvir/ledipasvir durant 8 setmanes. Dades de pràctica clínica.

Dades de pràctica clínica del tractament amb sofosbuvir/ledipasvir 8 setmanes

A. Cachero[1]; X. Xiol[1]; T. Casanovas[1]; JM. Castellví[2]; A. Imaz[4]; J. Castellote; E. Dueñas[1]; K. Serra[1]; A. Amador[1]; N. Padullés[1]; C. Baliellas[3]

[1]Servei de Digestiu. Hospital Universitari de Bellvitge - IDIBELL; [2]Servei de Digestiu. Hospital de Mataró; [3]Servei de Farmàcia. Hospital Universitari de Bellvitge - IDIBELL; [4]Servei de Malalties Infeccioses. Hospital Universitari de Bellvitge - IDIBELL

Temàtica: 4. Hepatitis

Introducció:

El tractament amb sofosbuvir/ledipasvir durant 8 setmanes es pot considerar en pacients infectats pel virus de l'hepatitis C (VHC) genotip 1 no cirròtics, naïve i amb càrrega viral basal inferior a 6 milions. Les dades de pràctica clínica disponibles inclouen un baix nombre de pacients amb fibrosi fase 3 (F3).

Objectiu:

Avaluar l'aplicabilitat i l'eficàcia del tractament amb sofosbuvir/ledipasvir durant 8 setmanes en pacients infectats pel VHC Genotip 1.

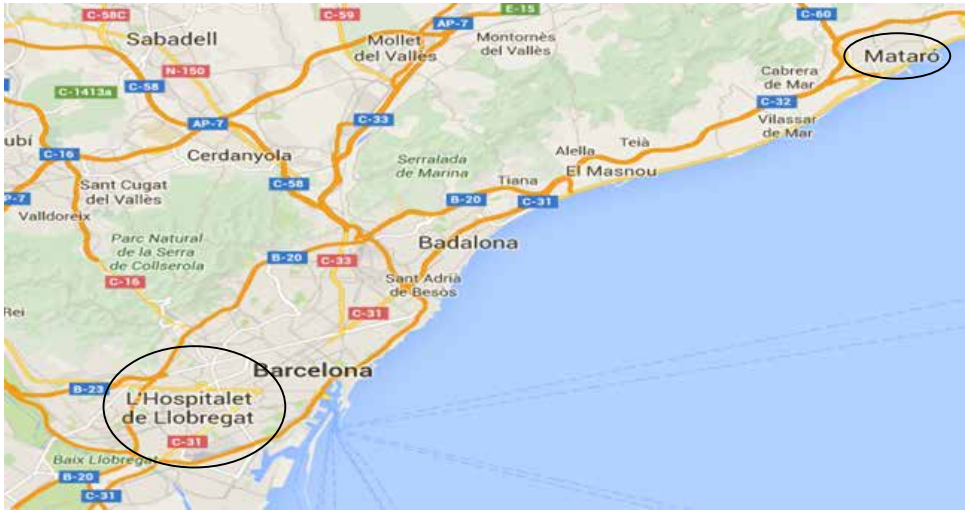
Mètodes:

S'han inclòs tots els pacients que d'abril a octubre 2015 han iniciat sofosbuvir 400mg/ ledipasvir 90mg durant 8 setmanes a l'Hospital Universitari de Bellvitge i a l'Hospital de Mataró. S'han recollit dades basals i seguiment a la fi de tractament, setmana 4 i 12 post-tractament.

Resultats:

De 66 pacients VHC genotip 1, no cirròtics i no trasplantats hepàtics, tractats durant el període d'estudi, 23 (35%) complien els criteris descrits i han rebut un tractament de 8 setmanes.

Característiques basals: 12 homes (52%), edat mediana 57 anys (28 -72); 3 pacients coinfectats per VIH i un pel VHB; grau de fibrosi basal: F1-F2 6 (26%) i F3 17 (74%), amb valor medià d'elastografia 10,5 kPa (4,1 – 11,8); genotip 1a/1b (30/70%); IL28B CT/TT 67%; càrrega viral basal mediana 974.000 (736-3.377.699).



23 pacients, RNA-VHC < 6 milions, naive
6 F0-F2, 17 F3, tractats 8 setmanes

RVS Setmana 4: 21/23 91,3%
per intenció de tractament

RVS setmana 4: 21/22 95,4%
per protocol

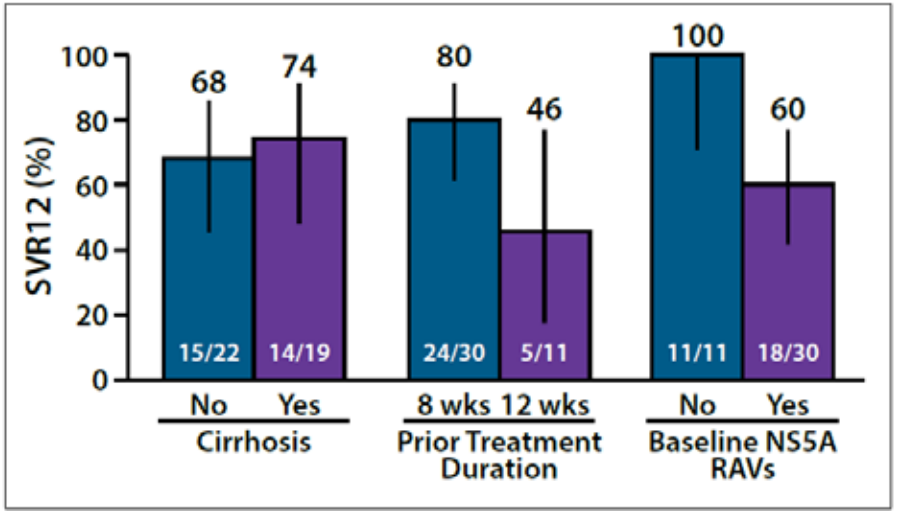
Cachero, Congres SCD 2015, oral C29

Sofosbuvir + Ledipasvir 8 setmanes

41 pacients tractats sofosbuvir + ledipasvir sense RVS
30: 8 setmanes; 11: 12 setmanes

Estudi resistències

NS5A RAV
- 19/30 (63%) 8 setmanes
- 11/11 (100%) 12 setmanes
NS5B RAV: 0%



Nou tractament 24 setmanes sofosbuvir + ledipasvir

29 RVS

12 NO RVS

Estudi resistències

12 NS5A RAV prèvia
NS5B RAV: 4 (33%)

Lawitz. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir -based regimes with an additional course of ledipasvir/sofosbuvir EASL 2015

Conclusions

- **Les cohorts en vida real demostren**
  - **Reproducibilitat del resultats obtinguts als assajos clínics**
  - **Altíssimes taxes de RVS a 8 setmanes (95%) similars a 12 setmanes (96%)**

- **Es confirma que el pacients que es poden beneficiar del règim de 8 setmanes:**
  - **No tractats prèviament**
  - **No cirròtics: F0-F3**
  - **Carga viral inferior a 6 milions**

- **Es constata que en les cohorts de vida real encara hi ha un grup important de pacients sobretractats i que es podrien beneficiar del regim de 8 setmanes (>50% en Target).**

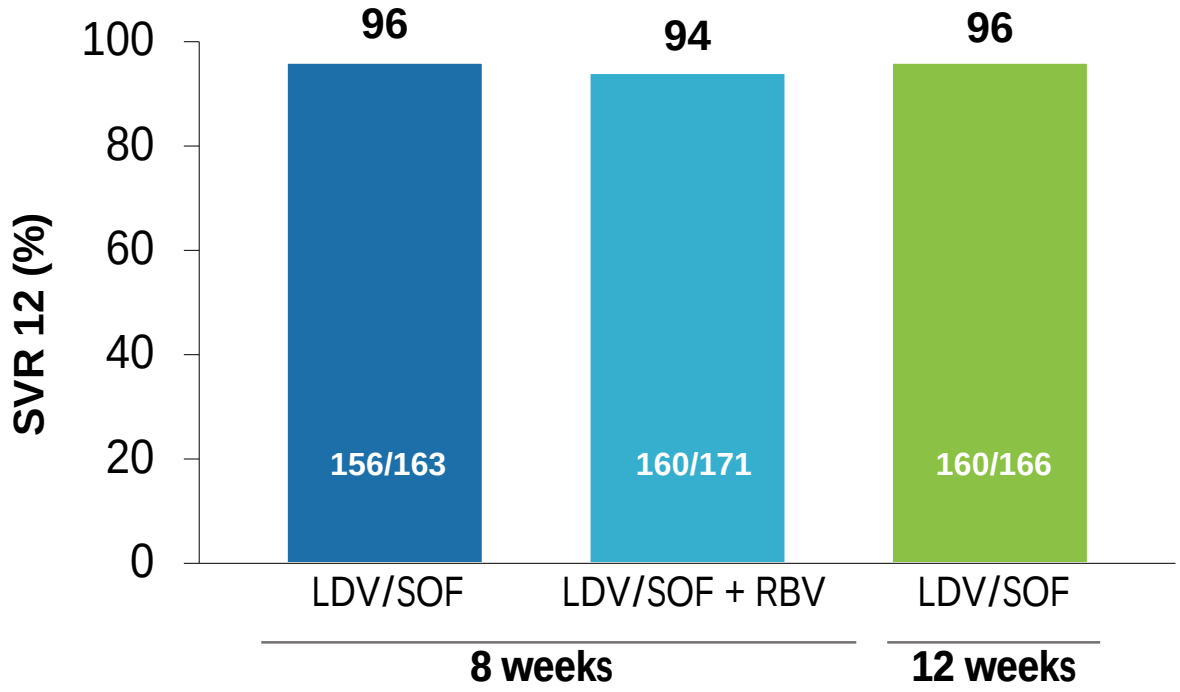
Conclusions

- **El fet de tenir CV detectable a la setmana 4, no influeix en la RVS12**
- **Els pacients F3 tenen taxes de resposta similar als F0-F2.**
- **Els pacients que no responen desenvolupen NS5A-RAV però no NS5B-RAV.**

- Back up

Sofosbuvir + Ledipasvir. ION3

Efficacy and Relapse in Subjects with Baseline HCV RNA < 10 Million IU/mL



	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 10M	**3.1% (5/163)**	4.1% (7/171)	1.2% (2/166)
Relapse Rates ≥ 10M	**11.5% (6/52)**	4.4% (2/45)	2.0% (1/50)

Wyles D. TUPEB249 IAS 2015

Sofosbuvir + Ledipasvir 8 setmanes

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

No Scientific Basis to Restrict 8 Weeks of Treatment With Ledipasvir/Sofosbuvir to Patients With Hepatitis C Virus RNA <6,000,000 IU/mL

In an important article, Kowdley and colleagues demonstrated a sustained virological response (SVR) rate of 93.5% in an intention-to-treat analysis among hepatitis C virus (HCV) genotype 1–infected, treatment-naive patients without cirrhosis who received ledipasvir/sofosbuvir for 8 weeks in the ION-3 trial.[1] Furthermore, the authors found treatment for 8 weeks to be noninferior to 12 weeks of treatment with this regimen.[1] A subsequent efficacy analysis that excluded could be treated for 8 weeks, the substantial resulting health care savings would allow treatment of many more patients for the same overall cost. The US label for Harvoni stipulates that 8 weeks of treatment should be considered only for patients with an HCV RNA <6,000,000 (6.78 $\log_{10}$) IU/mL, a level which, to our knowledge, has not been used previously for any treatment decisions. Given the importance of this criterion, we examined its statistical basis.

O Brian TR et al. HEPATOLOGY 2016; . 63: 28-29