News from EASL 2016 and upcoming HCV therapies

Sanjay Bhagani

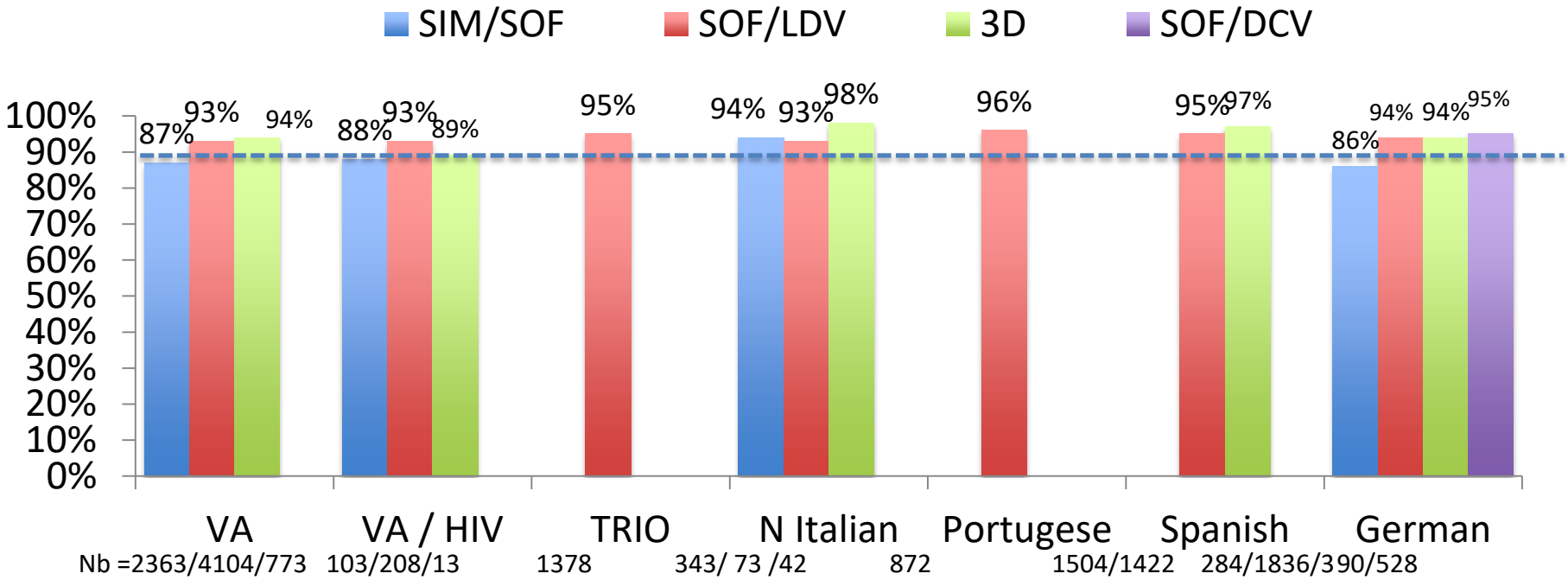
Royal Free London/UCL

Hepatology Highlights

Speaker Name	Statement
Sanjay Bhagani	Speaker Fees, Advisory Boards and Travel Grants from Abbvie, BMS, Gilead, Janssen and MSD
Date	June 2016

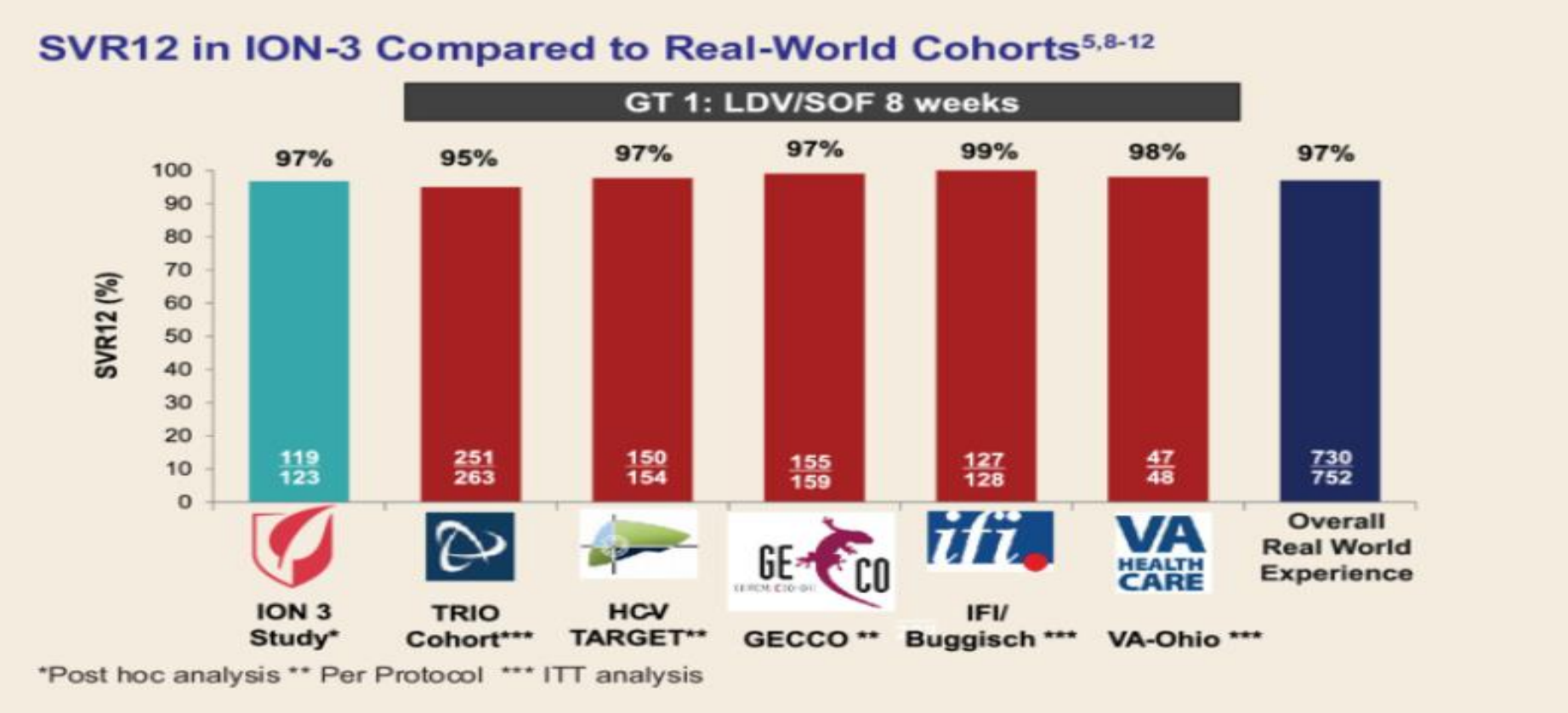
Real World Data

Large real-world data confirm clinical trial results: 16236 GT-1 patients



McCombs J et al: LBP-510,McGinnis J et al: LBP-514, Afdhal N et al: LBP-519, Aghemo A et al: LBP-500, Marinho T et al: LBP-523, Crespo J et al: LBP-511, Calleja JL et al: LBP-512, Mauss S et al: SAT-263

Real-world data confirm clinical trial results: 8 weeks in GT-1 patients without cirrhosis and VL< 6 millions IU/ml



Buggish P et al: SAT-242

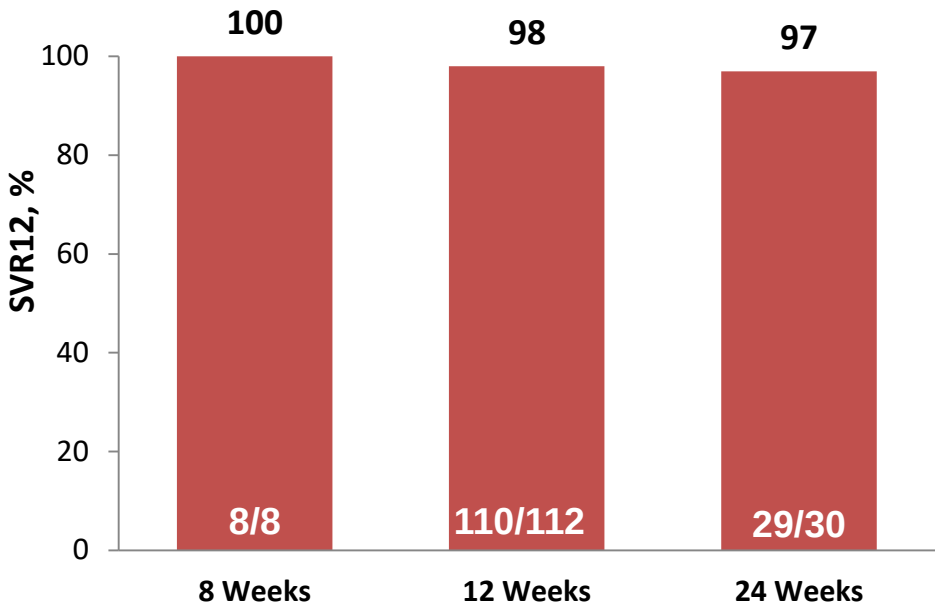
Real-world data in co-infected patients

LDV/SOF±RBV in 150 HIV/HCV Co-Infected Patients

Demographics

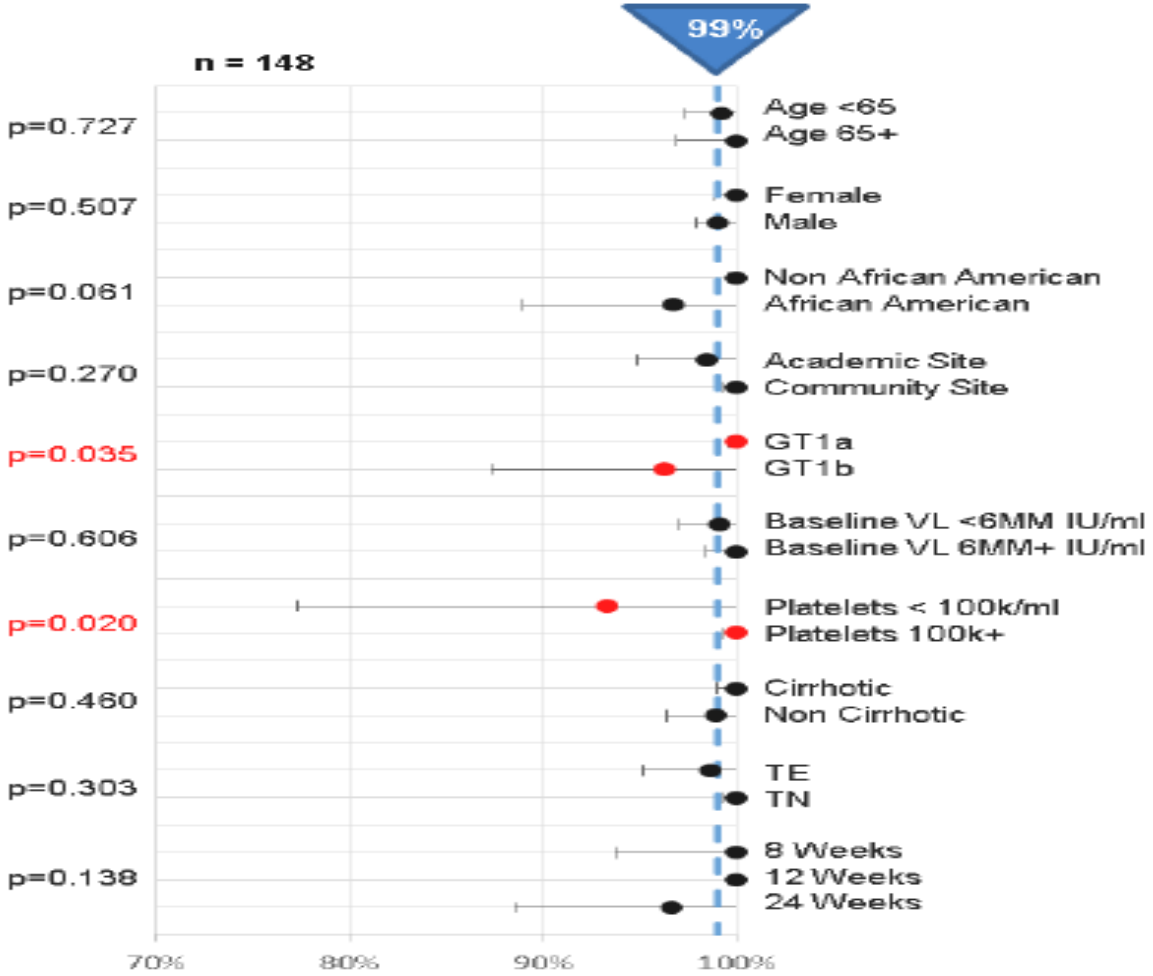
Patients, n (%)	Total N=150
Age, mean (range)	56 (36–84)
Academic practice	68 (45)
Male	105 (70)
Black	32 (21)
GT1a	120 (80)
Cirrhosis	53 (35)
Platelets <100,000/mL	15 (10)
Baseline RNA >6 MM IU/mL	32 (21)
Prior Treatment, n (%)	29 (19)
Prior Treatment unknown, n (%)	43 (28)
Treatment duration	
8	8 (5)
12	112 (75)
24	30 (20)

SVR12 by Duration (ITT)



High SVR rates achieved in the Real-World heterogeneous HIV/HCV-coinfected population

Dieterich, EASL 2016, Poster SAT-134

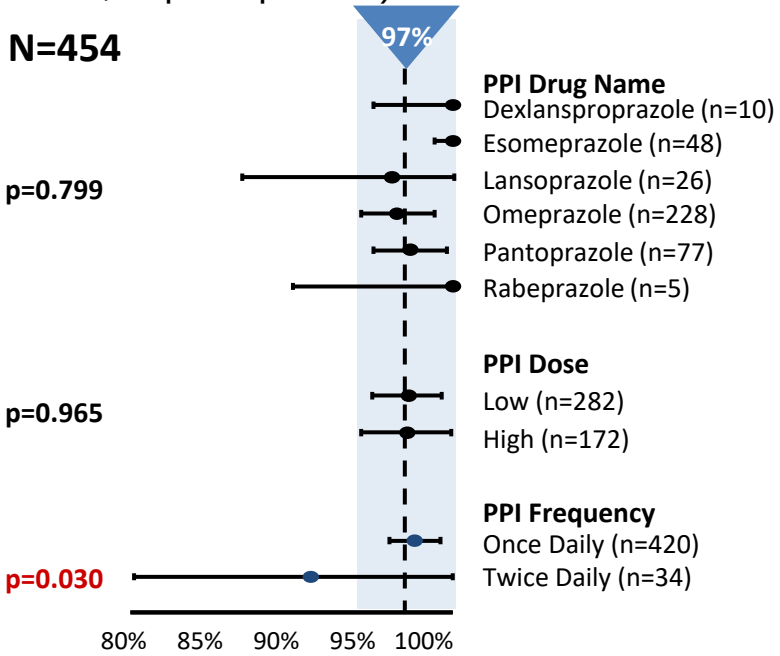


*Closed circles= proportions; whiskers = 95% confidence interval; dotted lines = overall SVR12; 2-side asympt. p-value via Pearson χ^2.

PPI use on LDV/SOF SVR in GT1 Patients

Predictors of response

- 38% (172/454) of the patients who were taking high-dose, and 7% (34/454) were on twice daily PPIs (omeprazole, esomeprazole, or pantoprazole)



Daily PPI use did not have an effect on SVR in a heterogeneous real-world US population when used according to US prescribing information

Afdhal, EASL 2016, LBP519

‘Real World’ data - conclusions

- Numerous datasets from ‘non-advanced’ liver disease treatment with DAAs – universally similar SVR12 rates to trial populations for both HCV mono-infected and HIV co-infected patients.
- No real ‘surprises’ in terms of predictors of response.
- Twice daily PPI use may have an effect on SOF/LDV response
- 8 weeks of SOF/LDV in non-cirrhotic G1 patients – gathering momentum

Treating patients with cirrhosis – benefits for all?

Antiviral treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/ daclatasvir, with or without ribavirin — outcomes compared to untreated patients and long term outcomes

Michelle CM Cheung[1], Graham R Foster[1], William L Irving[2], Alex J Walker[2], Benjamin E Hudson[3], Suman Verma[4], John McLauchlan[5], David J Mutimer[6], Ashley Brown[7], William TH Gelson[8], Douglas C MacDonald[9], Kosh Agarwal[4]

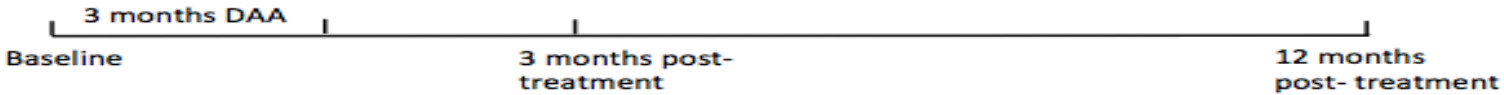
HCV Research UK

1. Queen Mary University of London 2. University of Nottingham 3. University Hospitals Bristol NHS Trust 4. King's College London 5. University of Glasgow 6. Queen Elizabeth Hospital, Birmingham 7. St Mary's Hospital, Imperial College London 8. Cambridge University Hospitals NHS Trust 9. University College London

EASL 2016, Barcelona

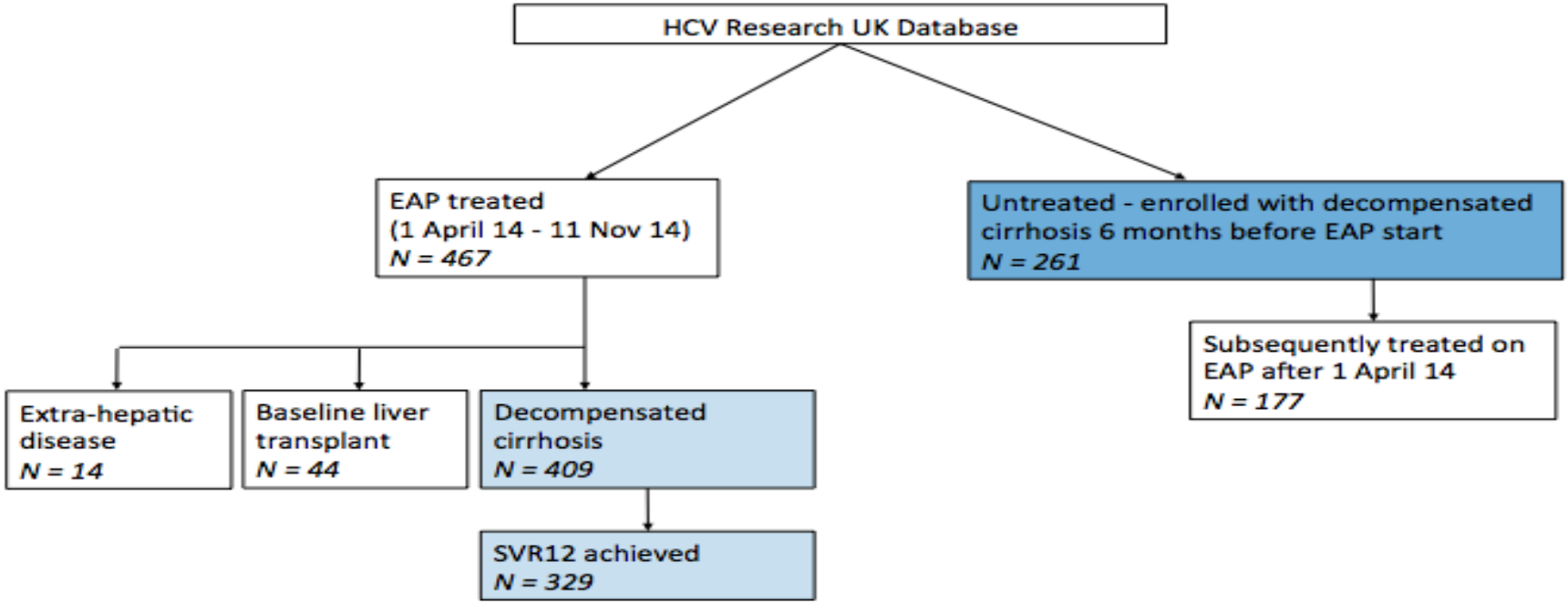
HCV Research UK

Method - Cohort Study



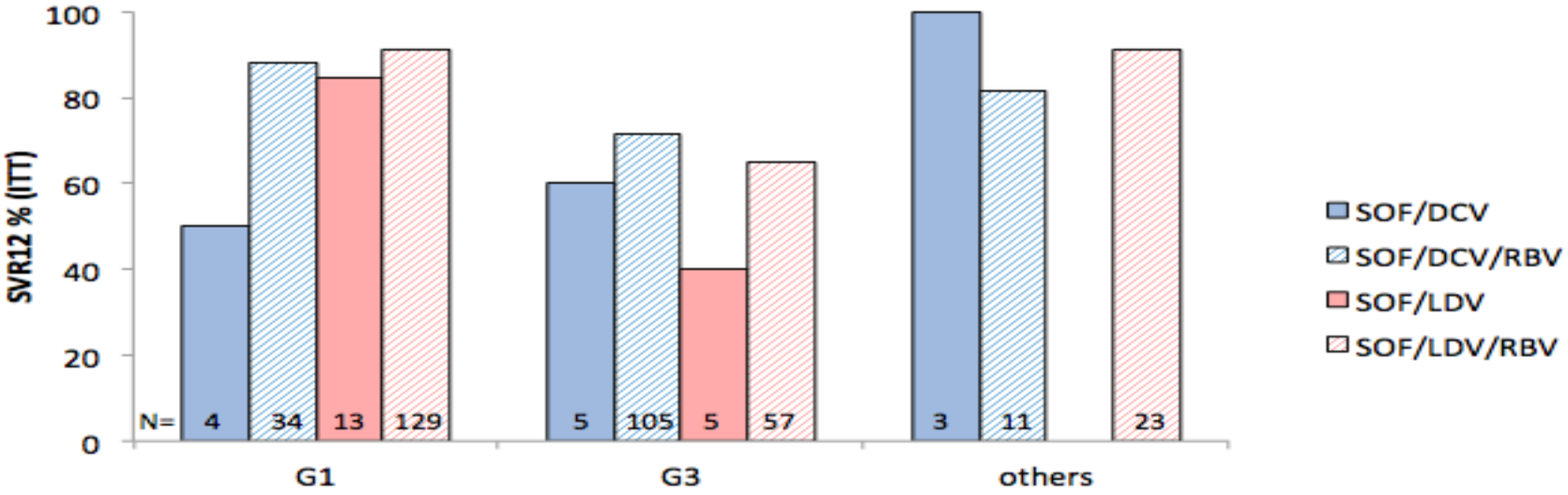
Patient Cohorts:

- EAP treated patients with baseline decompensation
- EAP treated patients with baseline decompensation who achieved SVR12
- Untreated patients with baseline decompensation

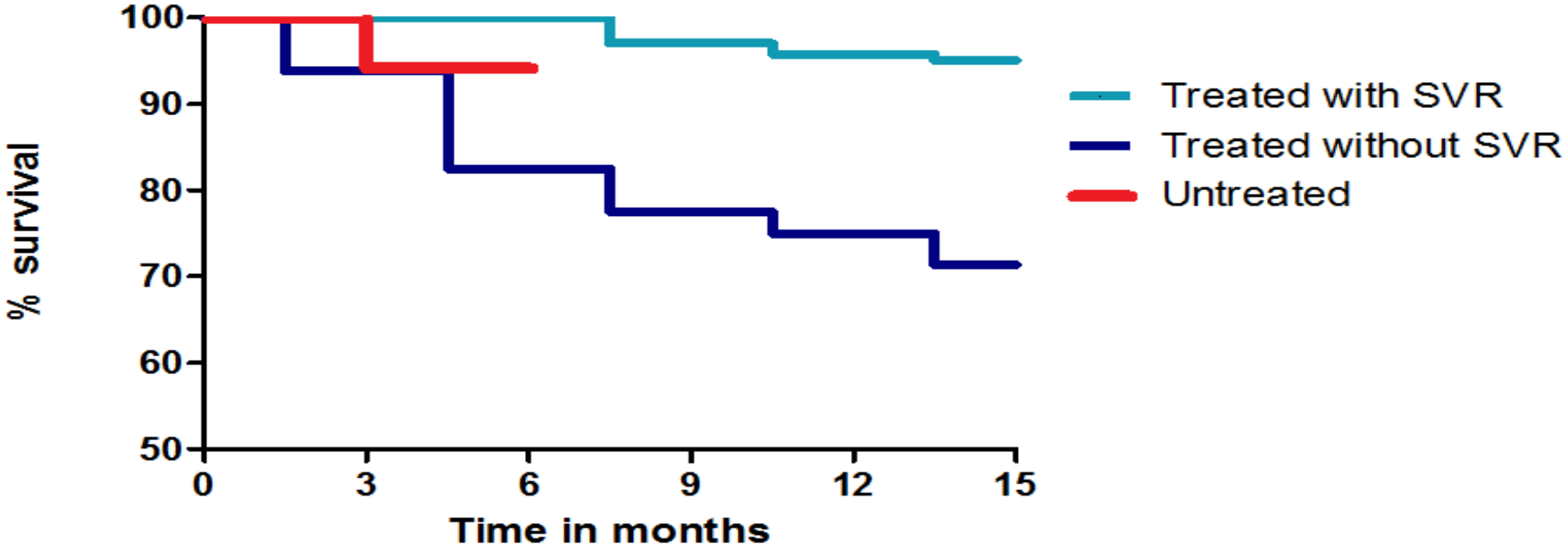

HCV Research UK Database
EAP treated
(1 April 14 - 11 Nov 14)
N = 467
Untreated - enrolled with decompensated cirrhosis 6 months before EAP start
N = 261
Subsequently treated on EAP after 1 April 14
N = 177
Extra-hepatic disease
N = 14
Baseline liver transplant
N = 44
Decompensated cirrhosis
N = 409
SVR12 achieved
N = 329

Results: Virological Outcomes

For patients with decompensated cirrhosis (N=409) – Overall SVR = 80.4%



Survival - Improved in SVR patients over non-SVR



Cheung, EASL 2016, Oral PS097

Adverse Events – first 6 months
Treated patients benefit

Event	All Treated (n=409)	Untreated (n=261)
Deaths	13 (3.2%)	15 (5.7%)
Decompensation	72 (17.6%)	73 (28.0%)*
New HCC	19 (4.6%)	21 (8.0%)
Sepsis	27 (6.6%)	15 (5.7%)
New OLT	27 (6.6%)	10 (3.8%)
Hospital admissions	133 (32.5%)	83 (31.8%)
MELD worsening >2	94 (23.0%)	99 (37.9%)*
Total adverse outcomes	213 (52.1%)	166 (63.6%)*

* $p < 0.05$ between treated and untreated

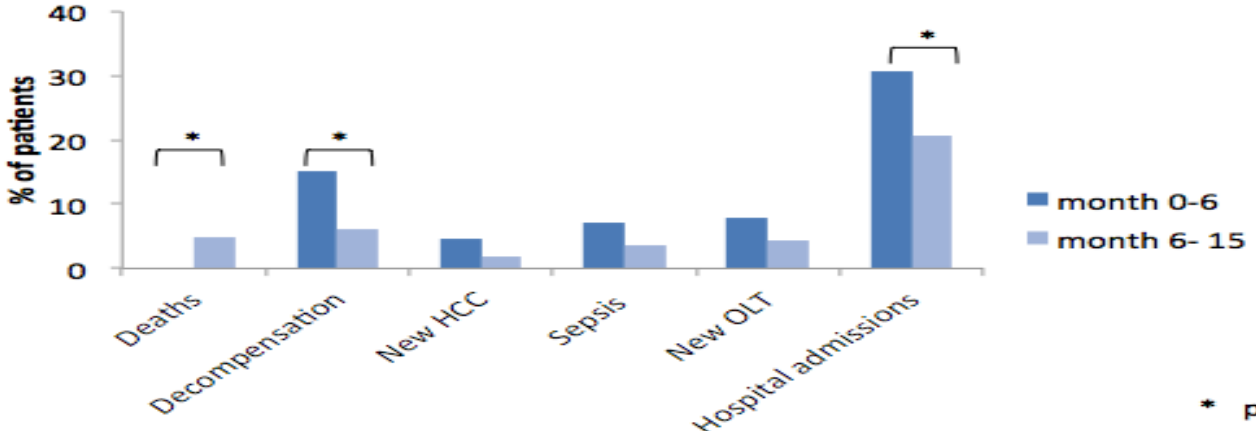
updated from Foster GR, Irving WL et al. J Hepatol 2016 Jan 29

The First 6 months

- Marked reduction in 'liver events' in treated patients compared with untreated
- Benefit in SVR patients rather than non-SVR [1]
- Is this sustained?

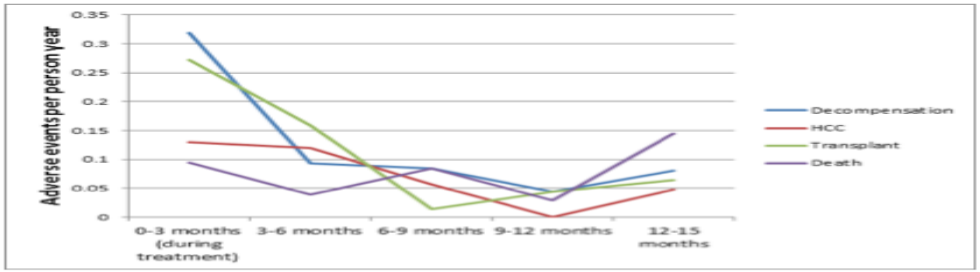
1. Foster GR, Irving WL et al. J Hepatol 2016 Jan 29

Adverse Events in 329 Virological Responders 15 months (3 months Rx, 12 months post-Rx)



* p< 0.05

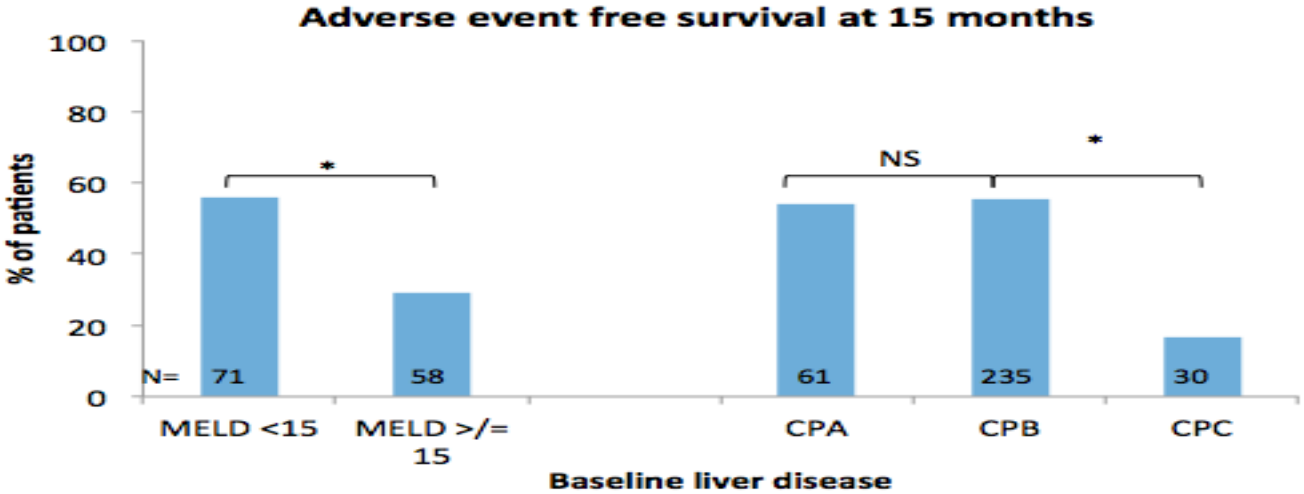
Adverse Events Over Time for Virological Responders – 15 months



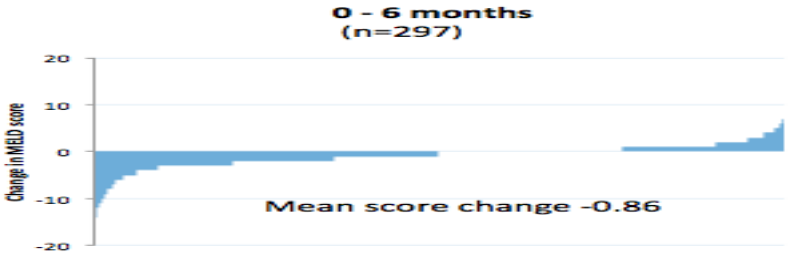
Overall in 329 patients over 15 months:

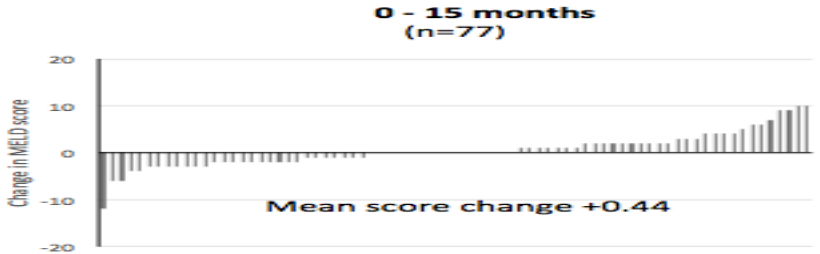
- Decompensation 21.3% (n=70)
- HCC 6.4% (21)
- Liver transplant 12.2% (40)
- Deaths 4.9% (16)

Which Patients Benefit from Viral Clearance?



MELD change – 6 & 15 months

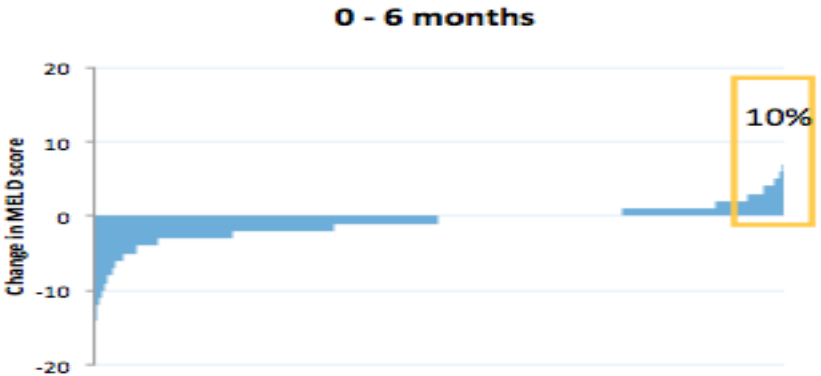


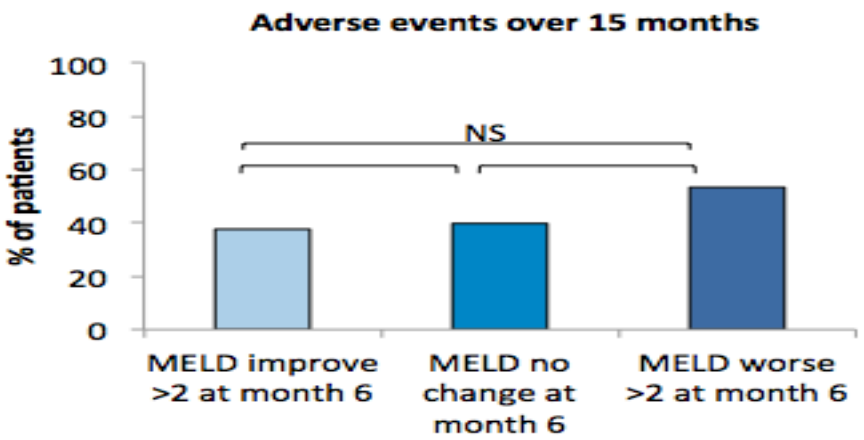


p< 0.05

Patients without SVR, transplanted or died were excluded

Does 'MELD Purgatory' exist?





Conclusions

- Antiviral therapy in patients with CP-B cirrhosis leads to prolonged improvement in the majority
- Only a minority of patients with CP-C cirrhosis derive long term benefit
- Early improvement does not necessarily translate into long term benefit

Division of
Gastroenterology and Hepatology
Department of Internal Medicine III

MEDICAL UNIVERSITY VIENNA
HEPATIC HEMODYNAMIC LAB

The evolution of portal pressure after viral suppression with interferon-free therapies and its correlation with the change in liver stiffness

Mattias MANDORFER[1, 2], Karin KOZBIAL[1], Philipp SCHWABL[1, 2], Clarissa FREISSMUTH[1], Rémy SCHWARZER[1, 2], Rafael STERN[1], David CHROMY[1], Thomas REIBERGER[1, 2], Albert F. STÄTTERMAYER[1], Wolfgang SIEGHART[1, 2], Sandra BEINHARDT[1], Michael TRAUNER[1], Harald HOFER[1], Arnulf FERLITSCH[1, 2], Peter FERENCI[1], Markus PECK-RADOSAVLJEVIC[1, 2]

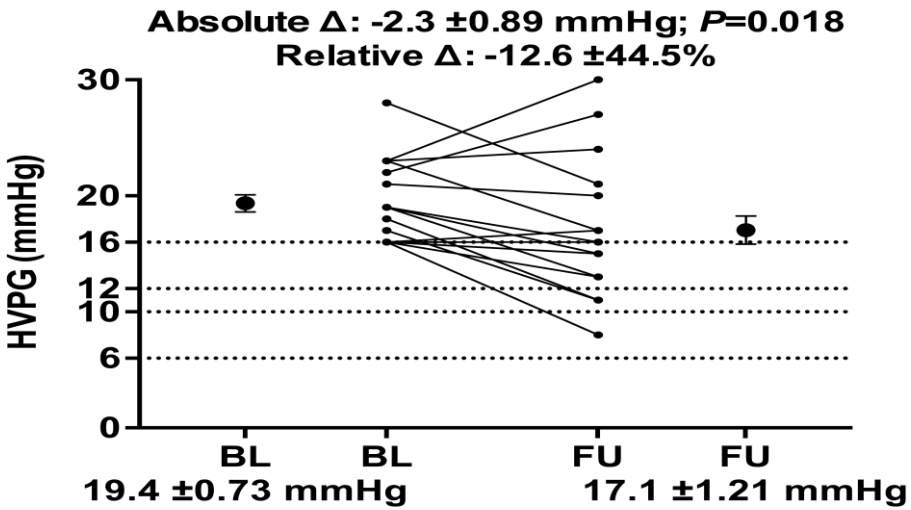
[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[3]Vienna Hepatic Hemodynamic Lab

Mattias Mandorfer and Karin Kozbial contributed equally to the work

Results

Δ HVPG: Pronounced portal hypertension at BL

- No patient resolved portal hypertension
- Regression to subclinical portal hypertension in 5% (1/20)
- FU HVPG of 10-15 mmHg in 35% (7/20)
- Increase in HVPG in 20% (4/20)



Conclusion – treatment of patients with advanced cirrhosis

- Comparatively lower SVR12 rates
- Higher risk of complications, de-compensation events in CP-C (data not shown)
- Benefit in most that achieve SVR12, but NOT ALL over a longer period of follow-up, especially CP-C, pronounced Portal Hypertension
- Improvement in MELD may not predict those likely to benefit

Real-world efficacy of generic DAAs

High sustained virological response rates using generic direct antiviral treatment for Hepatitis C

REDEMPTION-1

James Freeman[1], Richard Sallie[2], Adam Kennedy[3], Pham Thi Ngoc Nieu[1], John Freeman[4], Greg Jeffreys[5], Andrew M. Hill[6]

[1]GP2U Telehealth, Hobart, [2]Hepatology, Nedlands, [3]Kingswood Pharmacy, [4]Nephrology, Sandy Bay, [5]University of Tasmania, Hobart, Australia, [6]St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, United Kingdom

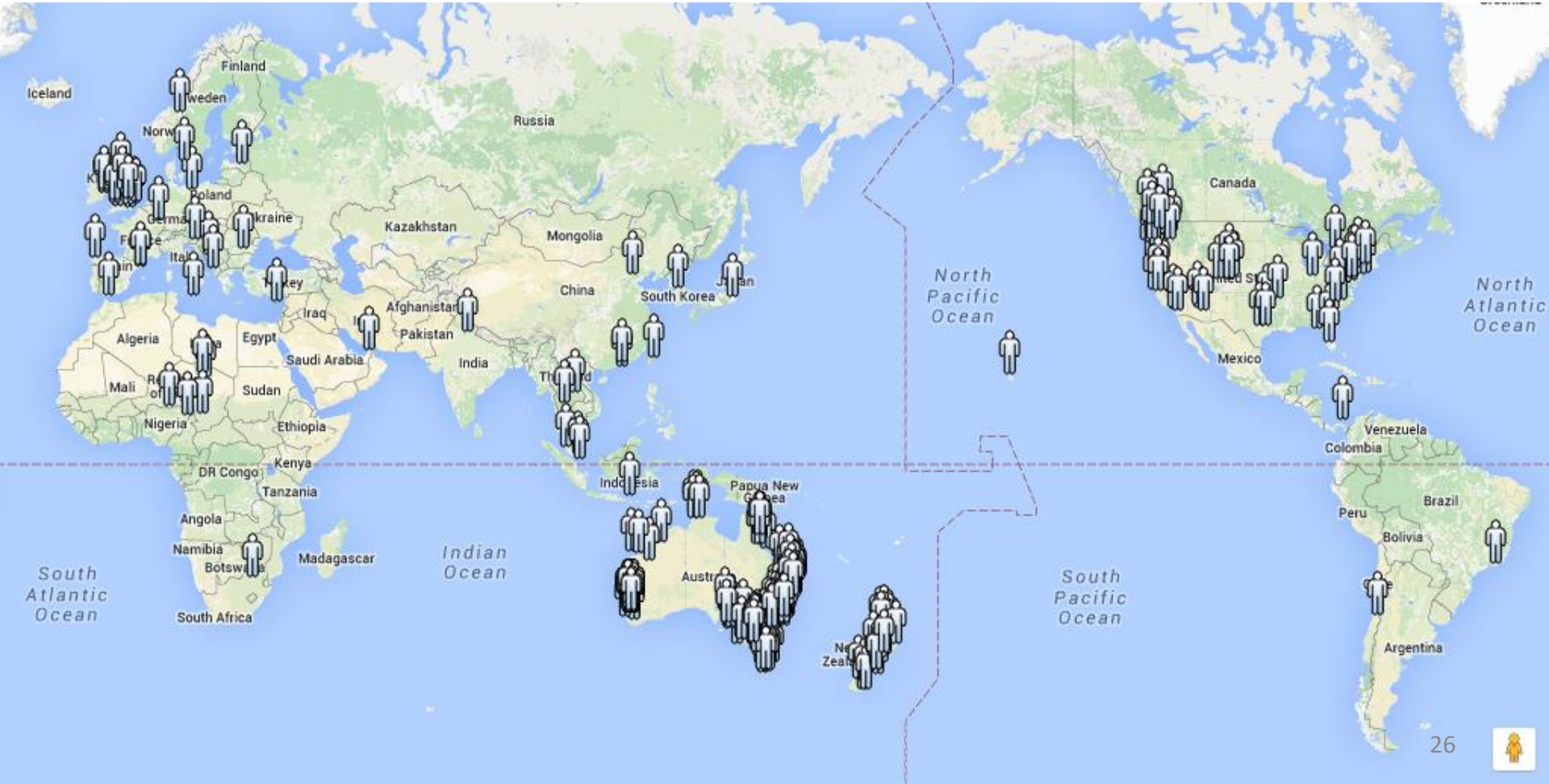
International Liver Congress 2016 13-18 April, Barcelona, Spain

LB03

The Legal Basis Of Personal Importation

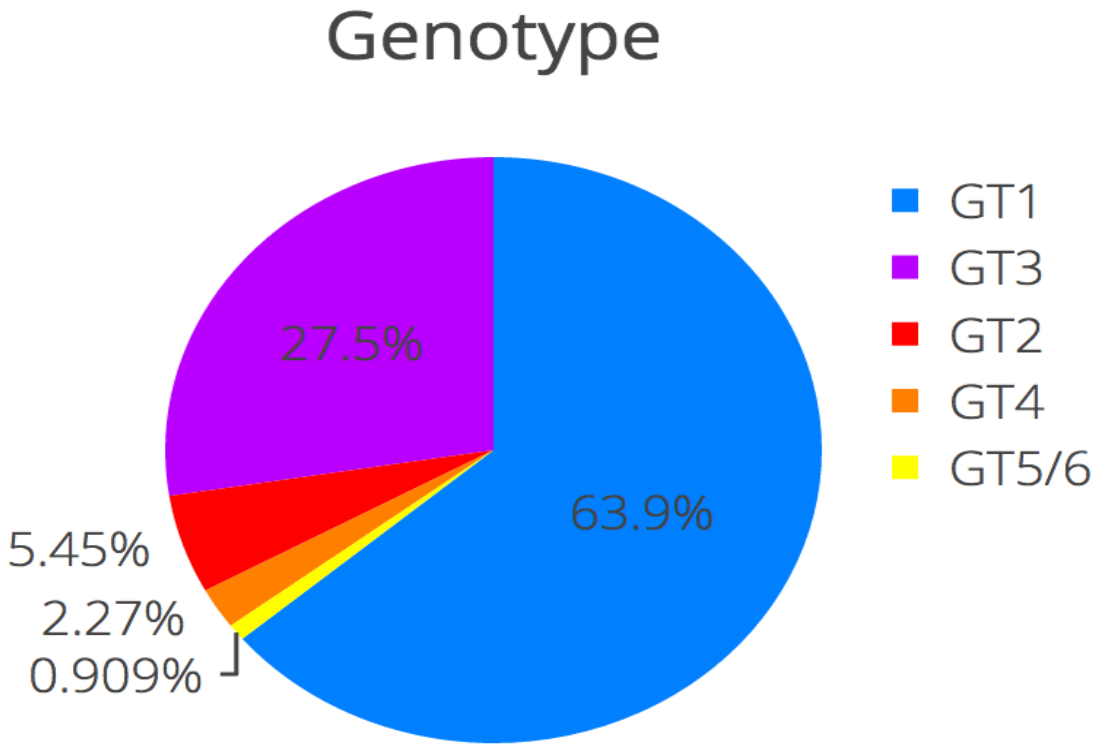
- Patents provision monopoly rights, however…
- Article 60 of TRIPS - De Minimis Imports – states:
  - *Members may exclude from the application of the above provisions small quantities of goods of a non-commercial nature contained in travellers' personal luggage or sent in small consignments*
- In line with Article 60 most countries allow some form of personal medication importation
- http://fixhepc.com/ helps patients access medication and discuss their treatment online

Redemption 1 - over 400 Patients Worldwide Enrolled (via fixhepC website)

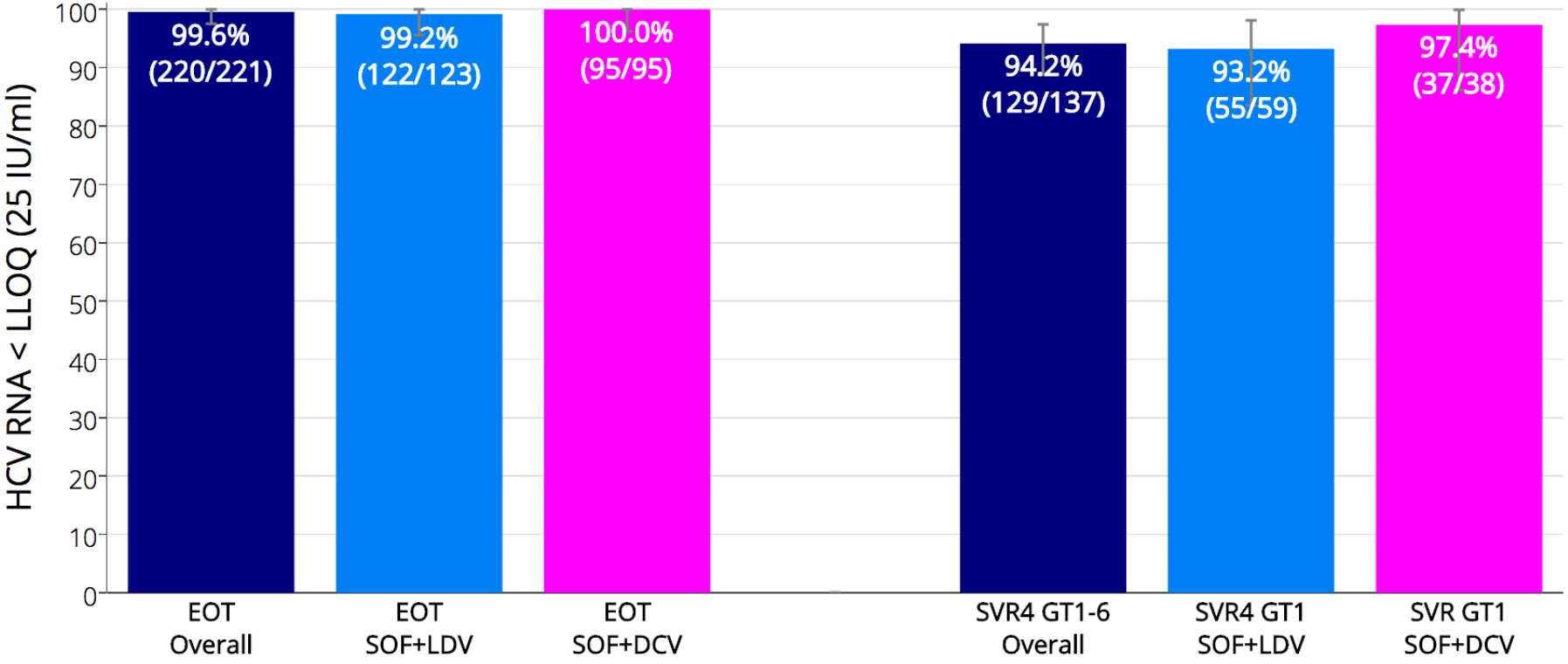


Baseline Characteristics

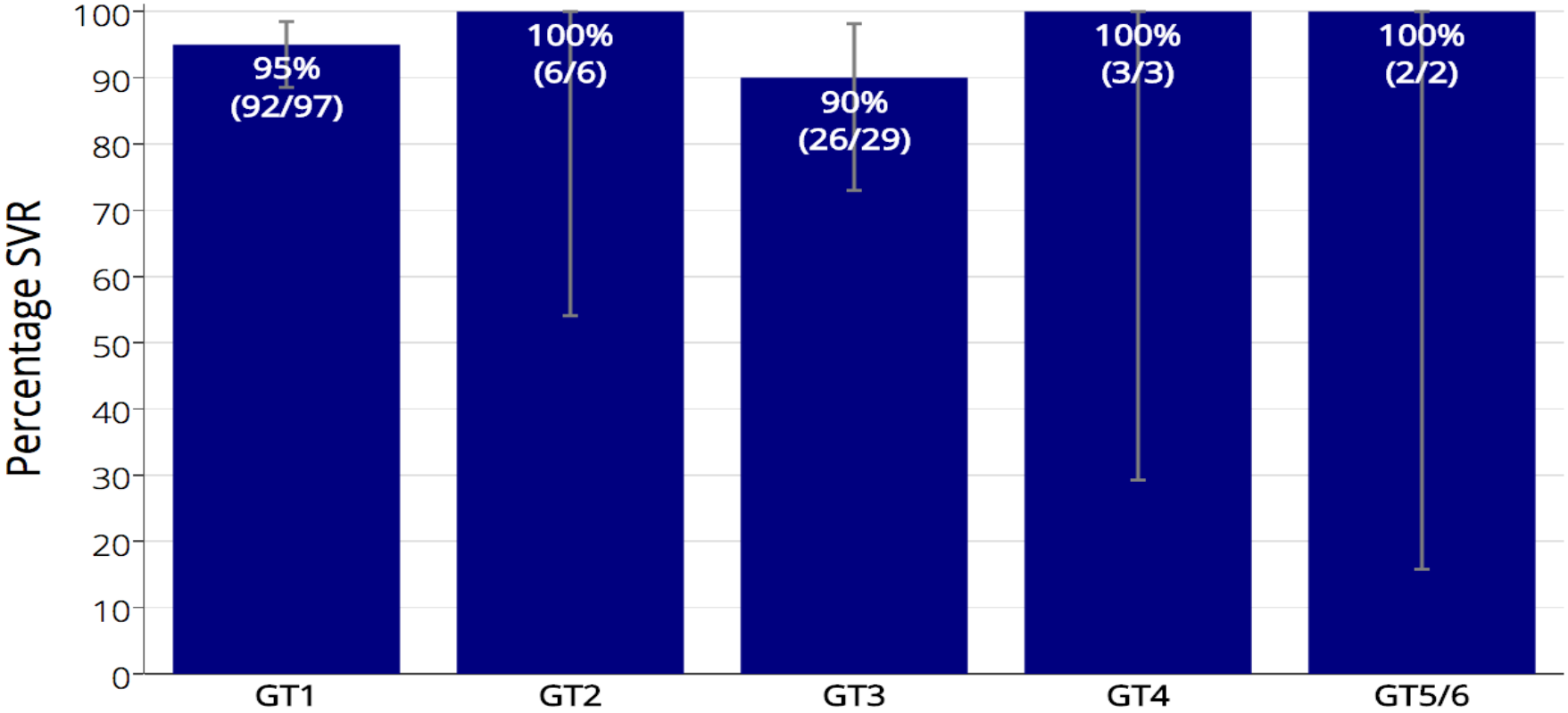
n	448
SOF+RBV	0.9% (4/448)
SOF+LDV	45.8% (205/448)
SOF+LDV+RBV	4.7% (21/448)
SOF+DCV	42.6% (191/448)
SOF+DCV+RBV	6.0% (27/448)
Naïve	51.6%
Cirrhosis	31.3%
Male	54.2%
Mean Age	54.4 years
Mean HCV RNA	6.46 log IU/ml 2878793 IU/ml



REDEMPTION-1 HCV RNA < LLOQ at EOT and SVR4



REDEMPTION-1 Overall SVR4 Results by Genotype



Note: Some small percentage loss of SVR is expected during the SVR4 to SVR12 period

Summary

- In this interim analysis, treatment with legally imported generic DAAs led to high SVR rates
- These SVR rates are similar to those seen in the Phase 3 trials of branded treatments
- Mass global treatment with generic DAAs is a feasible alternative where high prices prevent access to branded treatment

HCV Re-infection in HIV+ in Europe

Hepatitis C virus reinfection incidence and outcomes among HIV-positive MSM in Western Europe

Thomas Martin MD

On behalf of: Ingiliz P, Martin TCS, Rodger A, Stellbrink HJ, Mauss S, Boesecke C, Mandorfer M, Bottero J, Baumgarten A, Bhagani S, Lacombe K, Nelson M, Rockstroh JK and the NEAT study group

HCV reinfection among HIV positive MSM in Western Europe

- **Aims:**
  - **Primary: to calculate reinfection incidence among the European AIDS Treatment Network (NEAT) consortium centres in Western Europe (UK, Germany, Austria and France)**
  - **Secondary: to look for factors associated with reinfection and spontaneous clearance of reinfection**

HCV reinfection among HIV positive MSM in Western Europe

- Analysis:
  - Reinfection definition: newly positive HCV PCR any time after cure or earlier if HCV geno-/subtype switch occurred
  - Start of from end of treatment for those treated and the first negative HCV PCR for people who spontaneously clear
  - Date of reinfection taken as first newly positive HCV PCR
  - End of follow up - last negative HCV PCR
- Kaplan Meier survival methods.
- Comparison using log-rank and Cox proportional hazards
- Multiple logistic regression to assess factors associated with spontaneous clearance of reinfection

Overall population

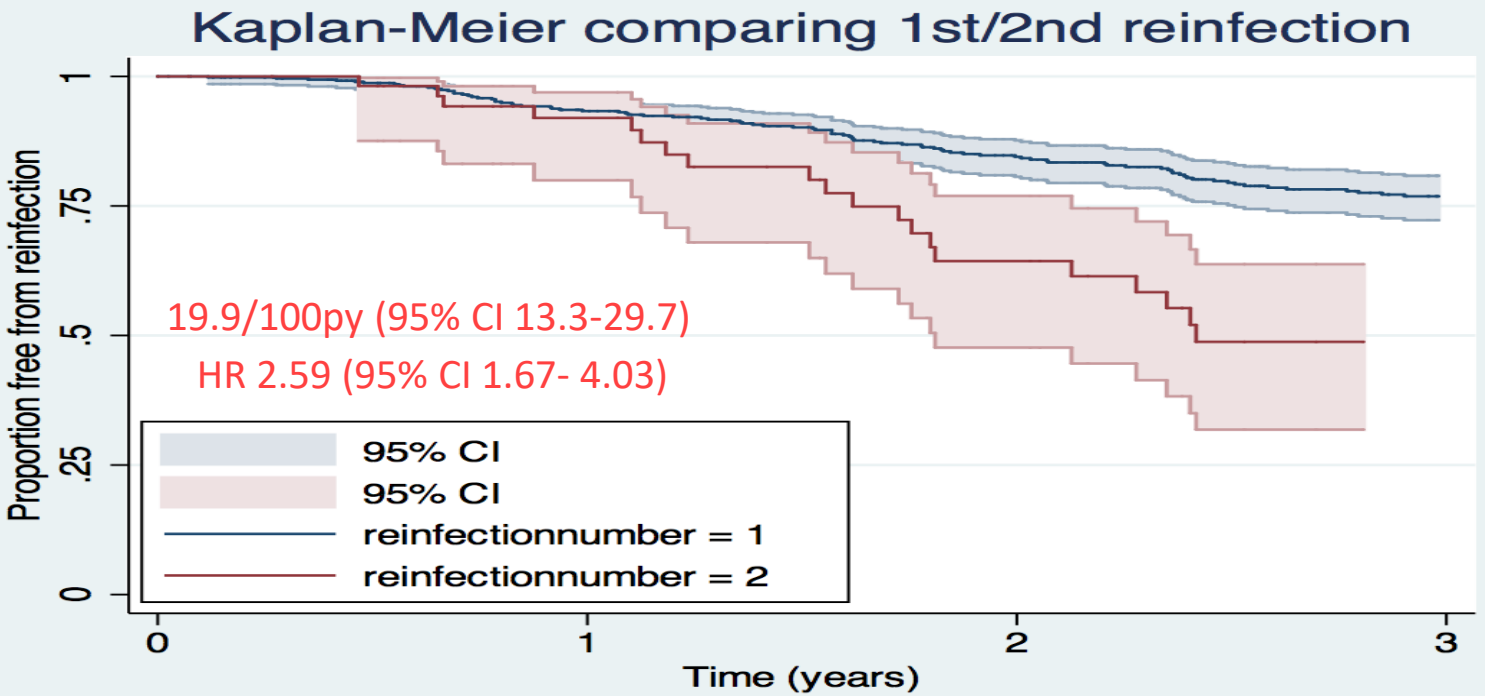
	Incident infection	1st Reinfection
Number included	606	606
Number reinfected (%)	N/A	149 (24.6)
Median time (years) to reinfection (IQR)	N/A	1.8 (1.1-3.2)
Genotypes (%)	GT1: 376(70.5) GT2: 13(2.4) GT3: 46(8.6) GT4: 96 (18)	GT1: 104(73.2) GT2: 1(0.7) GT3: 12(8.5) GT4: 25(17.6)
Genotype switches (%)	N/A	71/136 (52.2)
Median age at reinfection (IQR)	39 (34-44)	41 (37-45)
Median HIV duration at infection (only data for patients that were reinfected) (IQR)	5 (2-11)	9 (6-14)
Median CD4 at reinfection		553 (412-760)
Proportion with suppressed HIV VL		91/111 (82.0%)
SC proportion	111/605 (18.3%) (failed treatment not in denominator)	21/135 (15.6%)

113 treated with 87 achieving SVR (78%)

Overall population

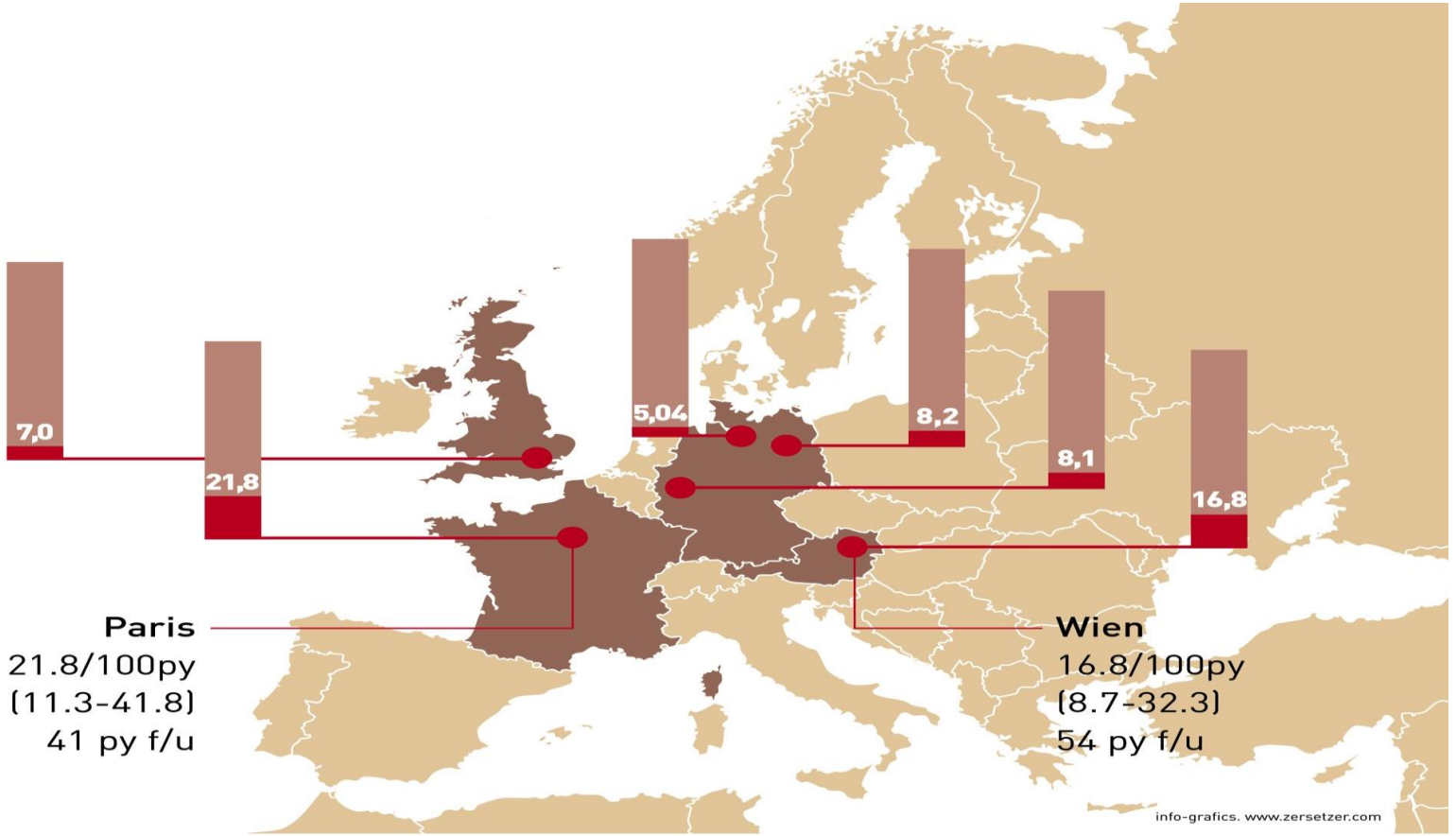
	2nd Reinfection	3rd reinfection	4th reinfection
Number included	69	13	2
Number reinfected (%)	29 (42.0)	4 (30.8)	1 (50)
Median time (years) to reinfection (IQR)	1.7 (1.2-2.4)		
Genotypes (%)	GT1: 22(84.6) GT2: 0 GT3: 1(3.8) GT4: 3(11.5)	GT1: 3(75) GT2: 0 GT3: 0 GT4: 1(25)	GT1: 1 (100) GT2: 0 GT3: 0 GT4: 0
Genotype switches (%)	13/25 (52.0)	2/4 (50)	1/1 (100)
Median age at reinfection (IQR)	43 (40-49)	-	-
SC proportion	6/21 (28.6%)	1/3 (33.3%)	0/1 (0%)

2nd Reinfection incidence is even higher than 1st reinfection



Number at risk				
Reinfection 1	482	405	313	219
Reinfection 2	56	40	24	12

Reinfection incidence by location



Conclusions

- **Substantial HCV reinfection risk among HIV/HCV coninfected MSM – 7.6/100 py with 25% reinfected at 3 years**
- **Failure of current prevention interventions**
  - **Urgently need prevention strategies**
- **Importance of rapid identification and treatment to prevent transmission of HCV or HIV**
  - **Suggest 3-6 month testing with HCV RNA PCR after initial infection**
  - **And every 3 months after a HCV reinfection**
- **Spontaneous clearance associated with reduced risk of reinfection (HR 0.55) and increased chance of spontaneous clearance if reinfected (OR 12.7)**

Can short-duration DAA-based therapy be used for acute/early HCV infection?

Recent data for shortened duration therapy in acute/early HCV in HIV+/-

Study	Genotype	Number	Regimen	Duration	SVR12 (%)
DAHHS[1]	1a	57	BOC + PegIFN/RBV	12 weeks	86
NYC[2]	1	19	TVR + PegIFN/RBV	12 weeks	84
CHAT[3]	1	9	TVR + PegIFN/RBV	12 weeks	56
DARE-C I[4]	1	14	TVR + PegIFN/RBV (Response Guided)	8/12/24 weeks	71
SWIFT-C[5]	1/4	17	SOF/RBV	12 weeks	59
DARE-C II[6]	1/3	14	SOF/RBV	6 weeks	21
NYC II[7]	1	12	SOF/RBV	12 weeks	92
SLAM-C Arm 1[8]	1	15	SOF/LDV	6 weeks	100
SLAM-C Arm 2[8]	1	15	SOF/SMV	8 weeks	100
SOL[9]	1	26	SOF/LDV	6 weeks	83

1. Hullegie, J Hepatol 2015; doi 10.1016/jhep.2015.12.004. [Epub ahead of print]. 2. Fierer, Clin Infect Dis; 2014; 58: 873-9. 3. Boesecke, unpublished (personal communication). 4. Martinello Antivir. Ther. 2016; doi 10.3851/IMP 3035 [Epub ahead of print] 5. Naggi, A1094, AASLD 2015, San Francisco CA. 6. Martinello, A1083, AASLD 2015, San Francisco CA. 7. Fierer, A1090, AASLD 2015, San Francisco CA. 8. Basu, A1074, AASLD 2015, San Francisco, CA. 9. Rockstroh, 154LB, CROI 2016, Boston, MA.

Six weeks of sofosbuvir/ledipasvir (SOF/LDV) are sufficient to treat acute hepatitis C virus genotype 1 monoinfection: The HepNet Acute HCV IV Study

Katja Deterding, Christoph Spinner, Eckart Schott, Tania Welzel, Guido Gerken, Hartwig Klinker, Ulrich Spengler, Johannes Wiegand, Julian Schulze zur Wiesch, Anita Pathil, Markus Cornberg, Andreas Umgelter, Caroline Zöllner, Stefan Zeuzem, Heiko von der Leyen, Dorothee von Witzendorff, Michael P. Manns, Heiner Wedemeyer

for the HepNet Acute HCV IV Study Group

Study design

- The German HepNet Acute HCV IV Study was designed as a single arm, prospective multicenter pilot study

10 centers in Germany recruited 20 patients
from Nov 2014 – Oct 2015

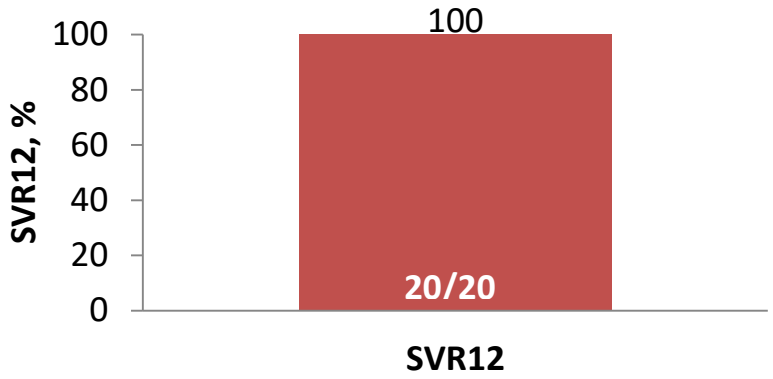
- München (C. Spinner)
- Berlin (E. Schott)
- Frankfurt (T. Welzel)
- Hannover (M. Manns)
- Würzburg (H. Klinker)
- Essen (G. Gerken)
- Leipzig (J. Wiegand)
- Heidelberg (A. Pathil)
- Bonn (U. Spengler)
- Hamburg (A. Lohse)

HEPNET Acute HCV IV Study

LDV/SOF for 6 Weeks in Acute HCV GT1

Baseline Demographics

	N=20
Male, n (%)	12 (60)
Age (years), mean (range)	46 (23-63)
HCV GT 1a	55
Risk factors for infection, n (%)	
Sexual transmission	11 (55)
Medical procedures/needle-stick injury	5 (25)
Nail treatment	1 (5)
Unspecified	2 (10)
ALT (U/l), mean (range)	463 (32 – 2716)
Bilirubin (mg/dl), mean (range)	24 (5.13 – 111)



	N=10
Drug-related AEs, n	22
AEs, n (%)	
GI	4 (20)
Fatigue	3 (15)
Hair loss	3 (15)
Headache	2 (10)
Skin reaction	2 (10)
Abdominal pain	2 (10)
Psychiatric disorders	2 (10)

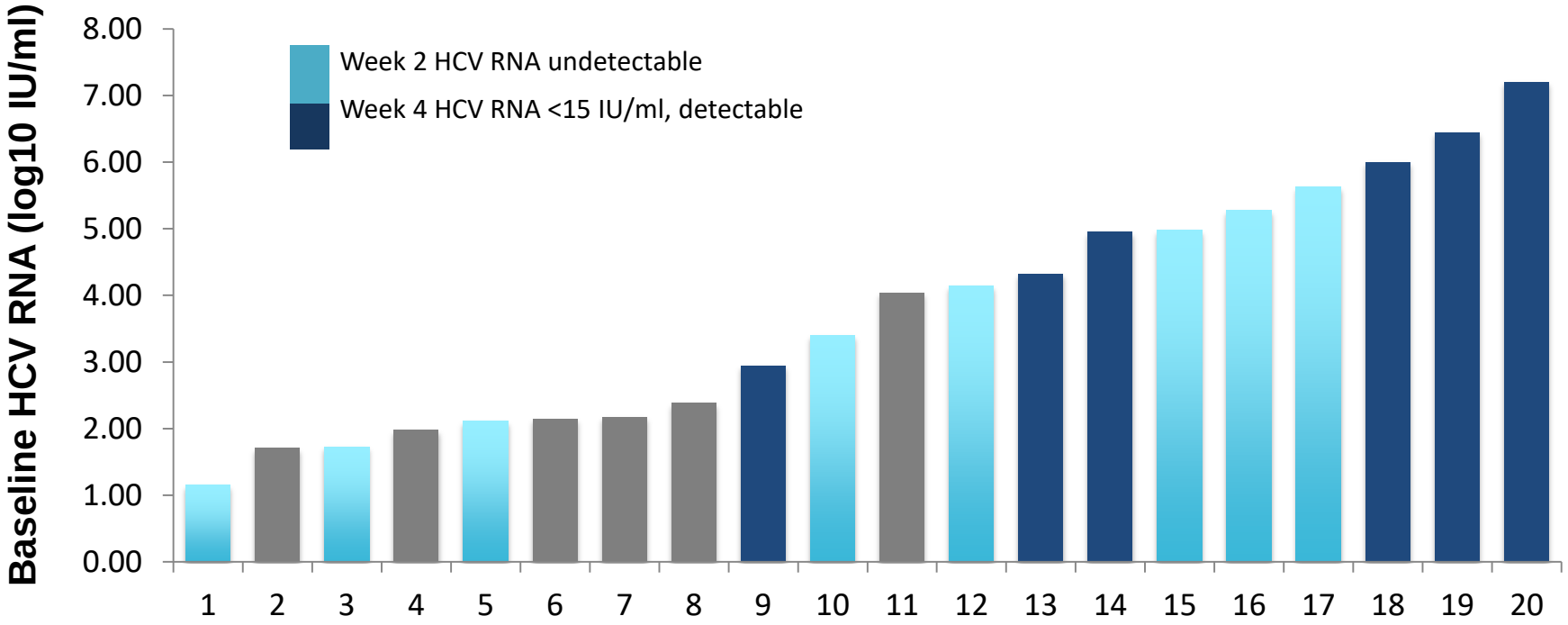
Short treatment of symptomatic acute HCV GT1 mono-infected patients with LDV/SOF 6 weeks was well tolerated with a rapid biochemical response

Deterding, EASL 2016, Oral LBO8

Harvoni▼ is not approved for the treatment of acute hepatitis C infection (HARVONI®▼ Summary of Product Characteristics, April 2016, Gilead Sciences, Europe)

LDV/SOF for 6 Weeks in Acute HCV GT1

Baseline HCV RNA and early virological response



Deterding, EASL 2016, Oral LBO8

Summary

- Treatment of symptomatic acute hepatitis C with sofosbuvir/ledipasvir (FDC) was safe and well tolerated
- Short treatment of only 6 weeks was highly effective with an SVR-12 rate of 100% in acute HCV genotype 1 mono-infected patients
- High baseline viral load was associated with a delayed virological response – which however did not lead to treatment failures
- A very rapid biochemical response was observed in patients with severe acute hepatitis C treated with an IFN-free regimen

New drugs? DAA failures?

HIGH SVR RATES WITH ABT-493 + ABT-530 CO-ADMINISTERED FOR 8 WEEKS IN NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 3 INFECTION

Andrew J Muir[1], Simone Strasser[2], Stanley Wang[3], Stephen Shafran[4], Maurizio Bonacini[5], Paul Y Kwo[6], David L Wyles[7], Edward Gane[8], Sandra S Lovell[3], Chih-Wei Lin[3], Teresa I Ng[3], Jens Kort[3], Federico J Mensa[3]

[1]Duke University School of Medicine, Durham, NC, USA; [2]AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown NSW, Australia; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]University of Alberta Hospital, Edmonton, AB, Canada; [5]California Pacific Medical Center, San Francisco, CA, USA; [6]Indiana University School of Medicine, Indianapolis, IN, USA; [7]University of California San Diego, La Jolla, CA, USA; [8]University of Auckland, Auckland, New Zealand

51st Annual Meeting of the European Association for the Study of the Liver
• Barcelona, Spain •
16 April 2016

abbvie

Next Generation Direct-acting Antivirals

ABT-493
Pangenotypic NS3/4A protease inhibitor

ABT-530
Pangenotypic NS5A inhibitor

In vitro:[1,2]
- High barrier to resistance
- Potent against common NS3 variants (eg., positions 80, 155, 168) and NS5A variants (eg., positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

ABT-493 identified by AbbVie and Enanta.

1. Ng TI, et al. Abstract 636. CROI, 2014.

2. Ng TI, et al. Abstract 639. CROI, 2014.

ABT-493 and ABT-530 Have Potent Activities Against All Major HCV Genotypes, Including GT3

Stable HCV GT3a Replicon EC_{50}			
NS3/4AProtease Inhibitor	nM	NS5A Inhibitor	pM
ABT-493	**1.6**	**ABT-530**	**2**
Grazoprevir[1]	35	Elbasvir[6]	140
GS-9857[2]	6.1	Velpatasvir[7]	20
Simeprevir[3,4]	472	Ledipasvir[8]	168,000
Paritaprevir	19	Ombitasvir	19
Asunaprevir[5]	1162	Daclatasvir[9]	530
		Odalasvir[10]	48
		MK-8408[11]	2

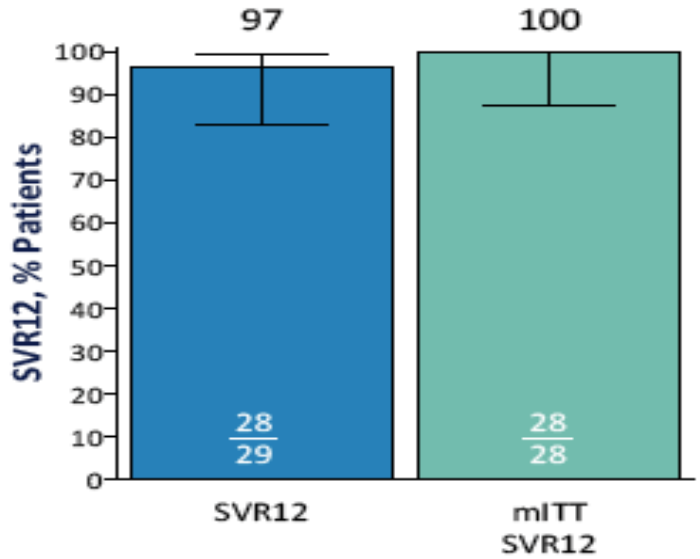
1. Lahser F, et al. AASLD, 2014.
2. Taylor J, et al. EASL, 2015.
3. Olysio prescribing information.
4. Chase R, et al. IAPAC, 2013.
5. McPhee F, et al. AAC, 2012.
6. Liu R, et al. AAC doi:10.1128/AAC.01390-15
7. Cheng G, et al. EASL, 2013.
8. Cheng G, et al. EASL, 2012
9. Wang C, et al. AAC, 2014.
10. ACHN R&D/Analyst Day
11. Asante-Appiah E, AASLD, 2014.

Demographics and Patient Characteristics

	ABT-493 + ABT-530 (N = 29)
Male, n (%)	15 (52)
Race, n (%)	
White	26 (90)
Black	1 (3)
Hispanic/Latino, n (%)	2 (7)
Age, mean years (range)	47 (27 – 66)
BMI, mean kg/m^2, ± SD	26 ± 3.8
HCV RNA, median log_{10} IU/mL (range)	6.5 (5.0 – 7.5)
HCV GT3a*, n (%)	25 (86)
Baseline fibrosis stage, n (%)	
F0 – F1	20 (69)
F2	2 (7)
F3	7 (24)

* Genotypes were determined using the Versant HCV Genotype Inno-LiPA Assay, version 2.0 or higher. Subgenotype (per the central lab) was not determined for 3 patients.

SVR12 Analysis



mITT SVR12 rate excludes non-virologic failures

No virologic failures

1 patient withdrew consent after treatment week 6 due to intolerance of blood draws and had an undetectable HCV RNA at the time of discontinuation

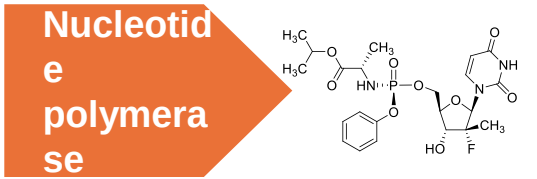
High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 for 12 Weeks in Treatment-Experienced Genotype 1–6 HCV-Infected Patients, Including Those Previously Treated With Direct-Acting Antivirals

Eric Lawitz[1], Kris Kowdley[2], Michael Curry[3], Nancy Reau[4], Mindie Nguyen[5], Paul Kwo[6], Ira Jacobson[7], Tram T. Tran[8], Ronald Nahass[9], Federico Hinestrosa[10], Robert Herring Jr.[11], Michael Bennet[12], Jenny C. Yang[13], Luisa M. Stamm[13], Di An[13], Hadas Dvory-Sobol[13], Diana M. Brainard[13], John G. McHutchison[13], Eugene Schiff[14], Mitchell Davis[15], Kyle Etzkorn[16], Raymond T. Chung[17], David Pound[18], Maribel Rodriguez-Torres[19], K. Rajender Reddy[20], Ziad Younes[21], Edward J.Gane[22]

[1]Texas Liver Institute, San Antonio, Texas, USA; [2]Swedish Medical, Seattle, Washington, USA; [3]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [4]Rush University Medical Center, Chicago, Illinois, USA; [5]Stanford University, Palo Alto, California, USA; [6]Indiana University School of Medicine, Indianapolis, USA; [7]Mount Sinai Beth Israel, New York, USA; [8]Cedars Sinai Medical Center, Los Angeles, California; [9]ID Care, Hillsborough, New Jersey, USA; [10]Orlando Immunology Center, Florida, USA; [11]Nashville Gastrointestinal Specialists Inc., Tennessee, USA; [12]Medical Associates Research Group, Inc., San Diego, California; [13]Gilead Sciences, Inc., Foster City, California; [14]University of Miami, Florida, USA; [15]Digestive CARE-South Florida Center of Gastroenterology, Wellington, Florida, USA; [16]Borland-Groover Clinic, Jacksonville, Florida, USA; [17]Massachusetts General Hospital, Boston, Massachusetts; [18]Indianapolis Gastroenterology Research Foundation, Indianapolis, Indiana, USA; [19]Fundación De Investigación De Diego, San Juan, Puerto Rico; [20]University of Pennsylvania , Philadelphia, USA; [21]Gastro One, Germantown, Tennessee, USA; [22]Auckland Clinical Studies, New Zealand

EASL 2016, Barcelona

Background



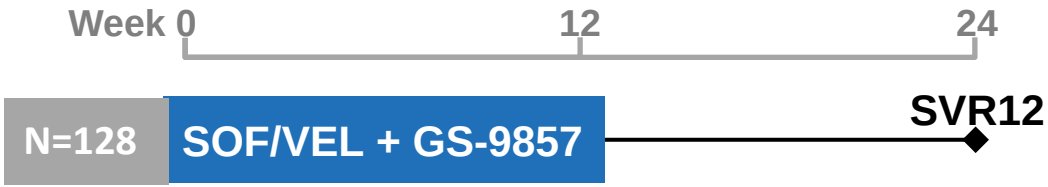
- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
- **Velpatasvir (GS-5816; VEL)[3-5]**
  - Picomolar potency against HCV GT 1–6
  - 2nd-generation NS5A inhibitor with improved resistance profile
- **GS-9857[6,7]**
  - HCV NS3/4A protease inhibitor with potent antiviral activity against HCV GT 1–6
  - Improved resistance profile compared with other HCV protease inhibitors
- **SOF/VEL + GS-9857**
  - SOF/VEL FDC (400/100 mg) tablet plus GS-9857 100-mg tablet is taken orally, once daily

FDC, fixed-dose combination

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. J Viral Hepat 2015;22:1011-9; 6. Taylor JG, et al. EASL 2015, poster 899; 7. Kirby B, et al. EASL 2015, poster 861.

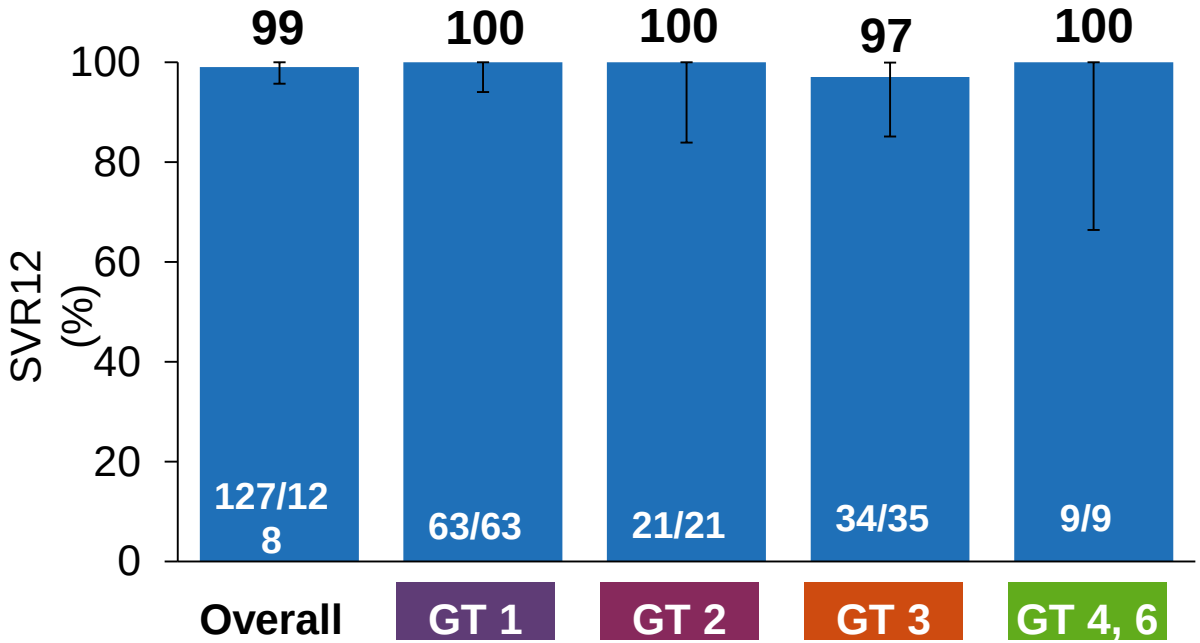
Study Designs

GS-US-367-1168 and GS-US-367-1169



- Two Phase 2, multicenter, open-label studies (US, New Zealand)
  - GS-US-367-1168: GT 1
  - GS-US-367-1169: GT 2, 3, 4, 5, 6
- Broad inclusion criteria
  - HCV treatment experienced, including DAA experienced
    - GT 1: NS5A inhibitor or ≥2 DAA classes
    - GT 2–6: Peg-IFN + RBV or any DAA
  - 50% with compensated cirrhosis

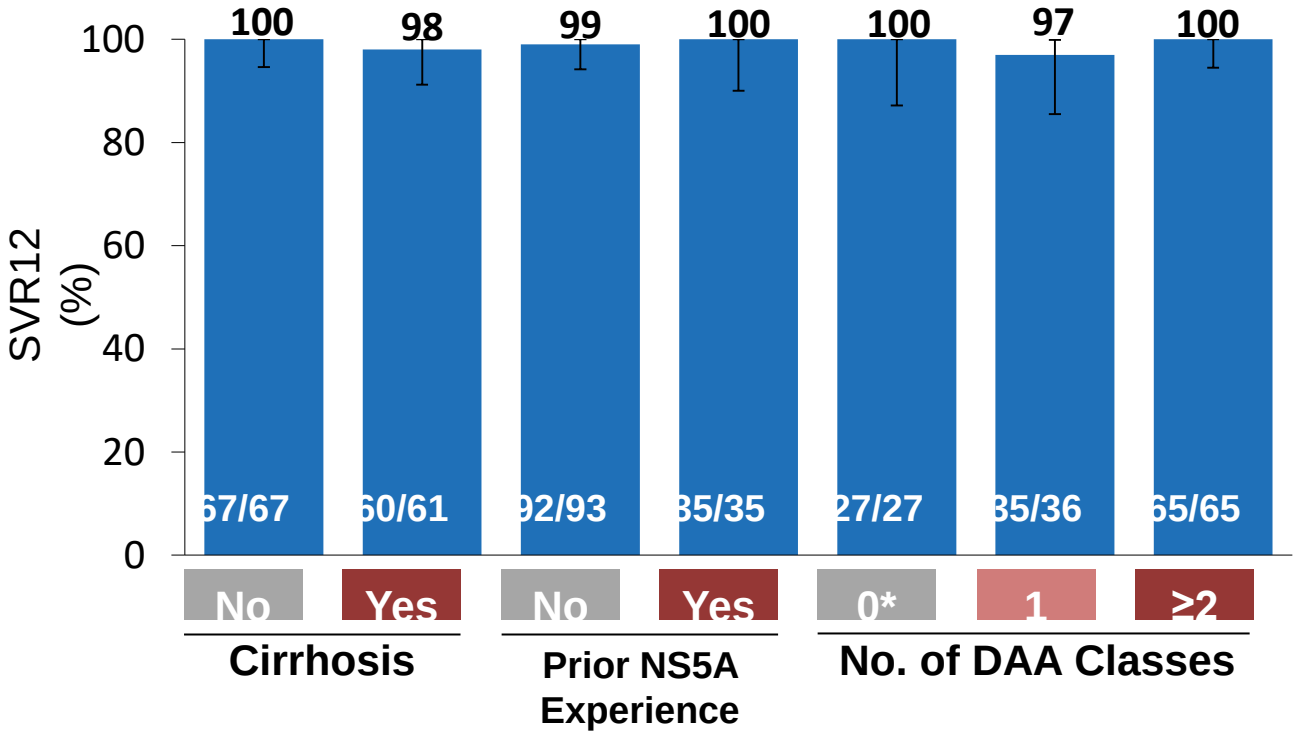
Results: SVR12 Overall and by Genotype



- One patient relapsed at post-treatment week 8

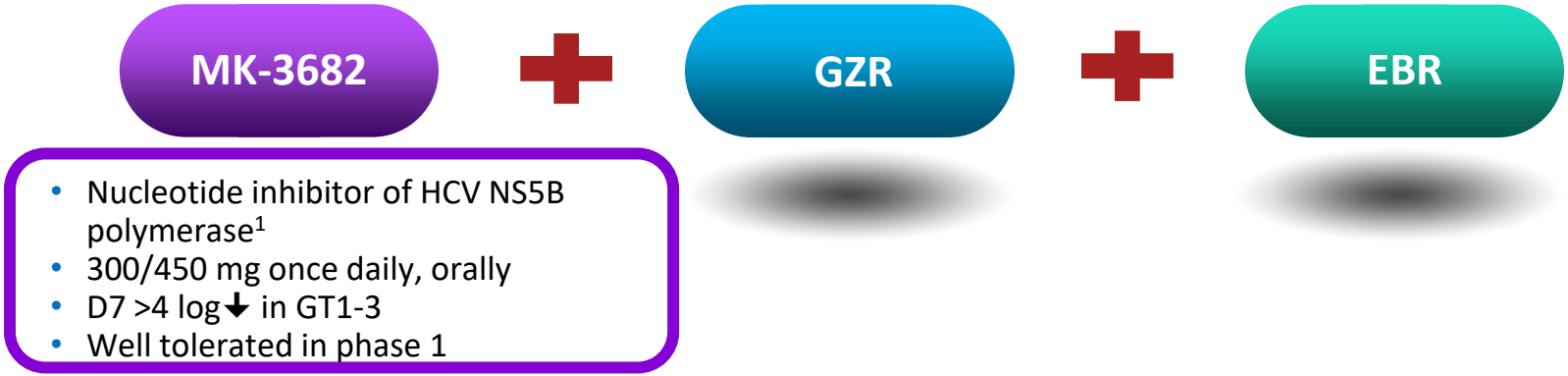
Error bars represent 95% confidence intervals.

Results: SVR12 by Subgroup



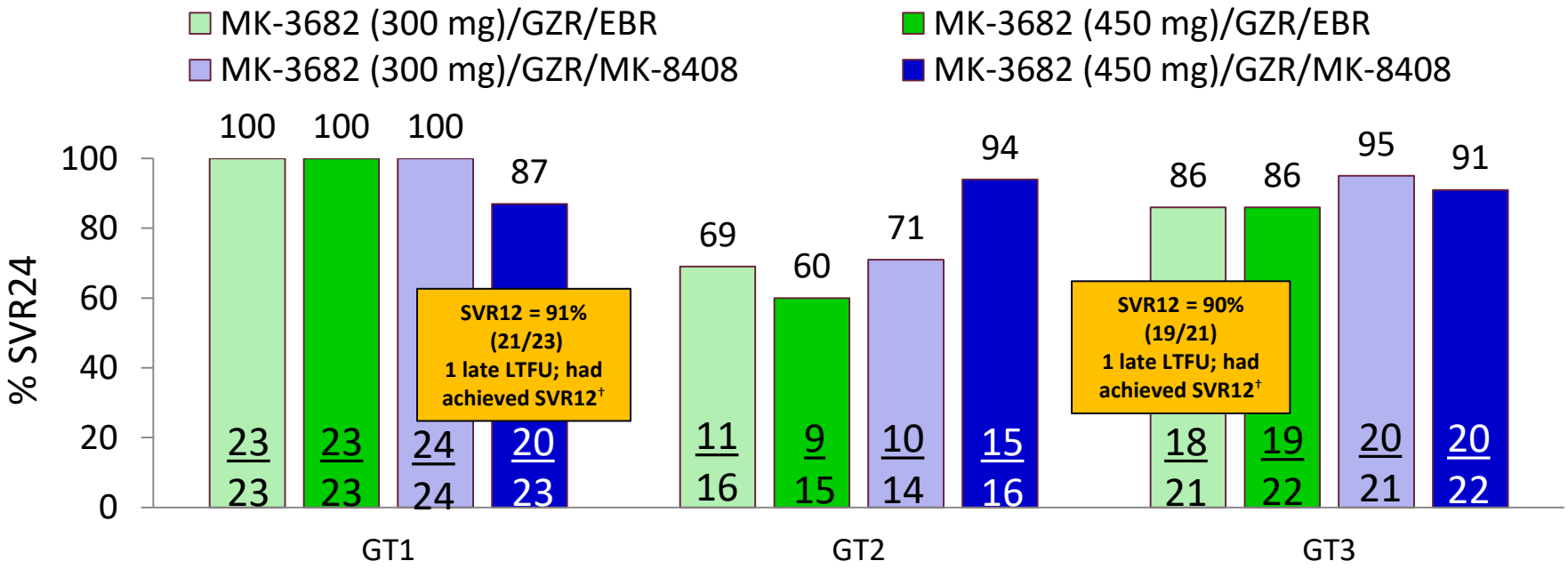
*GT 2-6 patients who failed prior Peg-IFN+RBV regimens.

MSD's 3-Drug Regimens in Part A of C-CREST 1 & 2: MK-3682 + GZR + EBR or MK-3682 + GZR + MK-8408



[1]Zhou et al., EASL 2015, Abst P0824; [2]Lahser et al., AASLD, 2014, Abst 1988; [3]Asante-Appiah et al., AASLD, 2014, Abst 1979

8 Week Regimen of MK-3682 (450 mg)/GZR/MK-8408 Achieved High SVR12 and SVR24 Rates in GT1, GT2 & GT3 (FAS*); No Virologic Failures between FW12 – FW24



*Primary efficacy: SVR12 of full analysis set (FAS); secondary efficacy: SVR24 of FAS. All 240 enrolled patients completed 8 weeks of treatment and reached follow-up 12 weeks after end of treatment. 2 subjects were lost to follow-up between FW12-FW24.

†One GT1b patient receiving MK-3682 (450mg)/GZR/MK-8408 and 1 GT3 patient receiving MK-3682 (300mg)/GZR/EBR were lost to follow-up between FW12-FW24; both had achieved SVR12.

Conclusions

- Next generation DAAs will be here soon
  - NS3/4 PIs
    - ABT-493 (Glecaprevir), GS-9857
  - NS5A
    - ABT-530 (Pibrentasvir) , MK-8408, PPI-668 (Ravidasvir)
  - NS5B
    - Nucleos(t)ides – MK-3682, AL-335
- Activity against G3, resistance to first-line DAA therapy

Acknowledgements

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