Update on Hepatitis C Therapy in CKD and ESRD

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Halifax, NS

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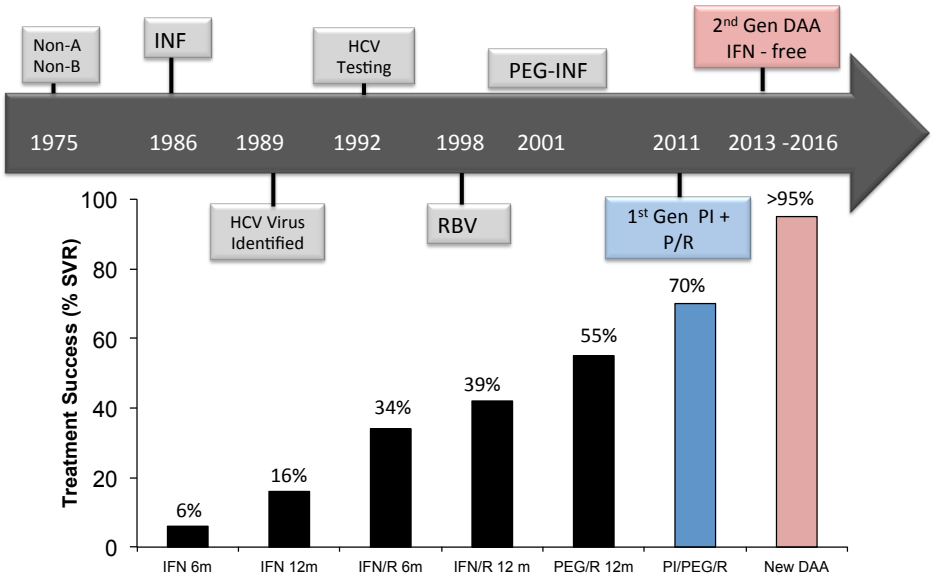
HCV Treatment Evolution



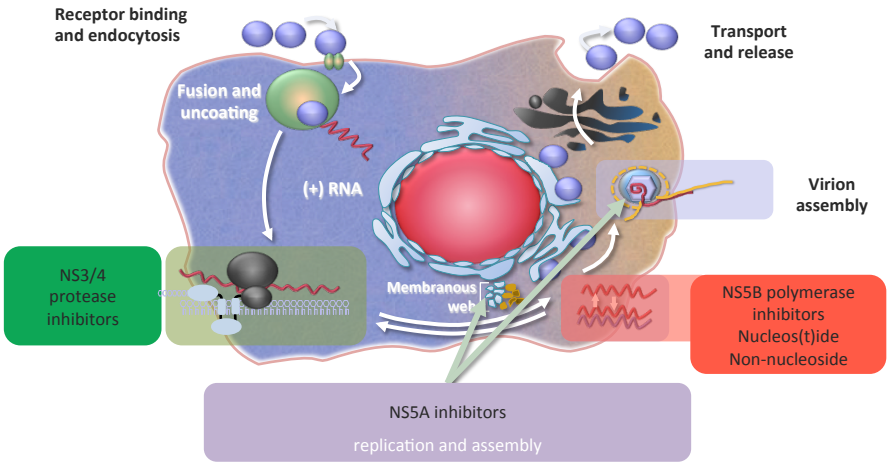
Contraindications to PEG-IFN & RBV

Up to 85% of patients have contraindications for IFN therapy!

- **Contraindications to PEG-IFN**
  - Decompensated cirrhosis
  - Autoimmune conditions
  - Major uncontrolled depressive illness
  - Untreated thyroid disease
  - Severe pancytopenia
    - ANC < 1.5, Plt < 90, Hgb < 100
- **Contraindications to RBV**
  - Pregnant or unwilling to comply with contraception
  - Significant cardiac disease
  - **Renal failure**

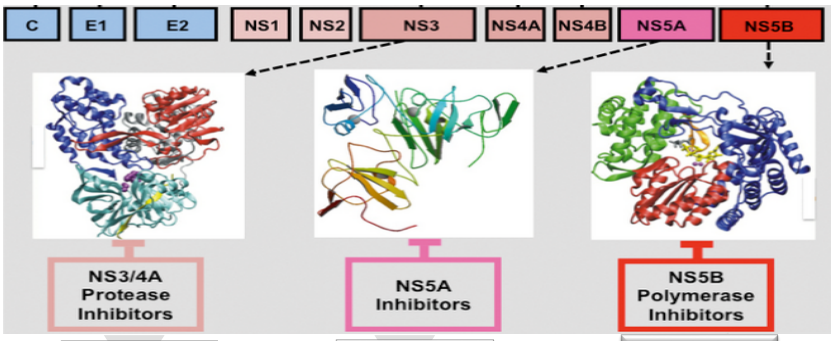
HCV Life Cycle

Targets for Direct-Acting Antivirals (DAAs)



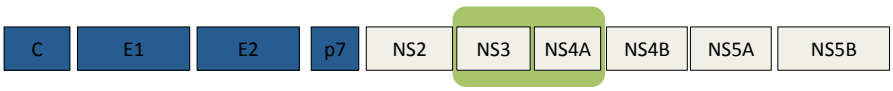
Adapted from Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000.

Classes of DAAs



"…PREVIR"	"… ASAVIR"	"…BUVIR"	
Telaprevir	**Ledipasvir**	**NUCS**	**NON-NUCS**
Boceprevir	**Ombitasvir**	**Sofosbuvir**	**Dasabuvir**
Simeprevir	**Daclatasvir**	VX-135	
Paritaprevir	**Elbasvir**	IDX20963	
Grazoprevir	Velpatasvir		
Sovaprevir	ACH-3102		
ACH-2684			

DDAs: Protease Inhibitors



High potency

Multigenotypic coverage

Low barrier to resistance

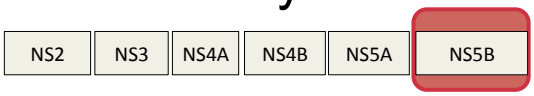
Not indicated for pts with moderate to severe hepatic impairment (Child-Pugh Class B or C)

ADR: rash, photosensitivity, fatigue, ↑ bilirubin

+++ Drug- Drug Interactions (CYP450 and Transporter proteins)

Telaprevir
Boceprevir
Simeprevir
Paritaprevir/r
Grazoprevir
Sovaprevir
ACH-2684

DDAs: Polymerase Inhibitors



NS5B Nucleos(t)ide Inhibitors (NI)

Sofosbuvir
VX-135
IDX20963

Intermediate potency

Pangenotypic coverage

High barrier to resistance

Minimal Drug interactions (P-gp substrate - Rifampin, antiepileptics and St John's Wort

ADR: fatigue, nausea, headache

Renally eliminated -Not recommended in pts with mod-severe renal impairment – CrCl < 30ml/min

NS5B Nonnucleoside Inhibitors (NNI)

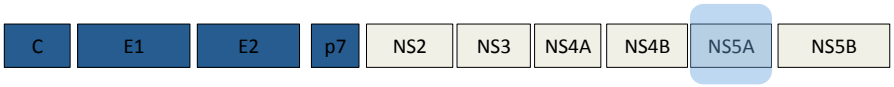
Dasabuvir

Intermediate potency

Limited genotypic coverage

Low barrier to resistance

DDAs: NS5A Inhibitors



High potency

Multigenotypic coverage

Low barrier to resistance

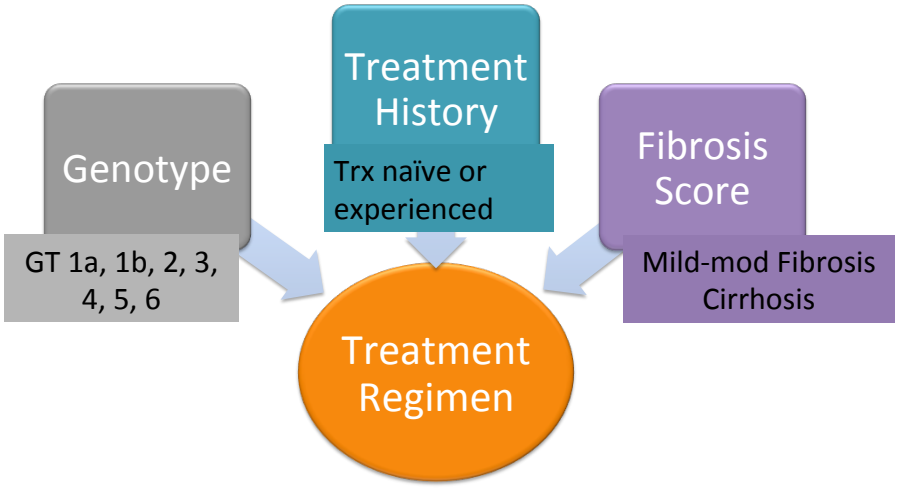
DI: Transporter proteins

Acid reducing therapy with LDV

ADR: Unknown

Ledipasvir
Ombitasvir
Daclatasvir
Elbasvir
Velpatasvir
ACH-3102

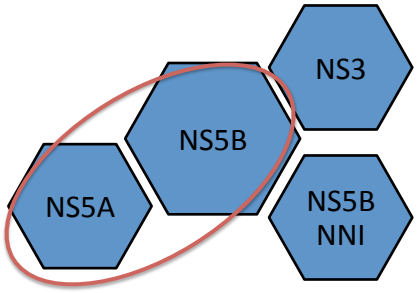
Factors Determining Treatment Regimen



Health Canada

APPROVED HCV COMBINATION REGIMENS

HARVONI®
Ledipasvir(NS5A)/Sofosbuvir(NS5B)



Ledipasvir/Sofosbuvir (Harvoni®)

- **Approval Status**:
  - Health Canada Approval 10/16/14
  - FDA Approval 10/10/14
  - European Approval 11/18/14
- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotype 1, 4, 5, 6 in adults
- **Class & Mechanism**
  - Ledipasvir: NS5A inhibitor
  - Sofosbuvir: Nucleotide analog NS5B polymerase inhibitor
- **Dosing:** Ledipasvir-Sofosbuvir (fixed dose 90 mg/400 mg) One tablet orally once daily with or without food -Single Tablet Regimen (STR)
- **Adverse Effects (AE)**: Fatigue, headache

ION-1,2,3: SOF/LDV FDC +/- RBV

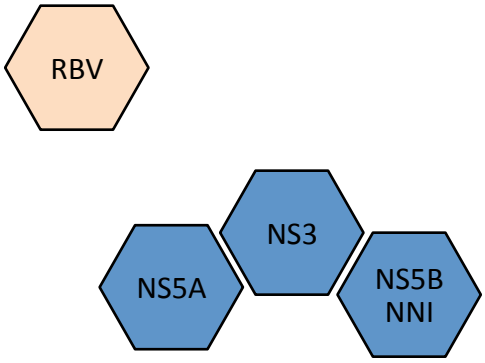
Phase III Studies, R, Open Label
once-daily fixed-dose combination of SOF/LDV for 8, 12 or 24 weeks, +/- RBV N=1,952 GT 1 (TN, TE including failed 1st gen PI)

Study	Population	Treatment	Duration	SVR 12 Rates
ION-1* (n= 865)	GT-1 Treatment-naïve (16% with cirrhosis)	LDV/SOF	12 weeks	99% (211/214)
		LDV/SOF + RBV	12 weeks	97% (211/217)
		LDV/SOF	24 weeks	98% (212/217)
		LDV/SOF + RBV	24 weeks	99% (215/217)
ION-2+ (n= 440)	GT-1 Treatment-experienced (20% with cirrhosis)	LDV/SOF	12 weeks	94% (102/109)
		LDV/SOF + RBV	12 weeks	96% (107/111)
		LDV/SOF	24 weeks	99% (108/109)
		LDV/SOF + RBV	24 weeks	99% (110/111)
ION-3^ (n= 647)	GT-1 Treatment-naïve (0% with cirrhosis)	LDV/SOF	8 weeks	94% (202/215)
		LDV/SOF + RBV	8 weeks	93% (201/216)
		LDV/SOF	12 weeks	95% (206/216)

*NEJM 2014;370:1889-98; +NEJM 2014;370:1483-93; ^NEJM 2014;370:1879-88

HOLKIRA®: 3D Regimen

Paritaprevir/ritonavir-Ombitasvir + Dasabuvir (PrOD)

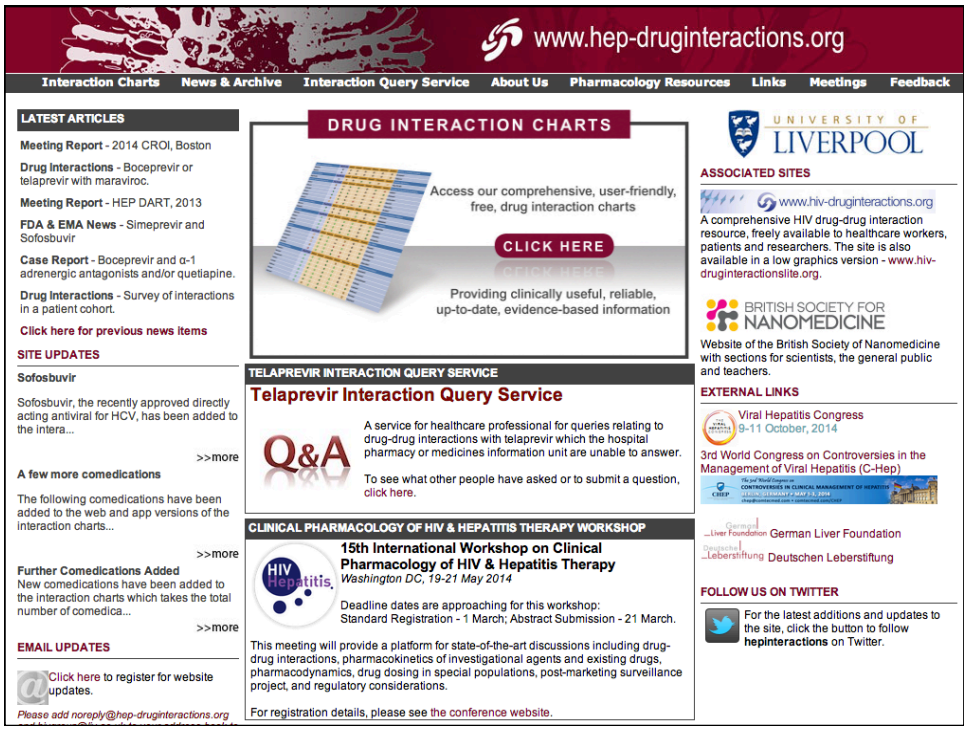


Paritaprevir/ritonavir-Ombitasvir + Dasabuvir

- **Approval Status:** FDA & Health Canada approval December 2014
- **Indication**: Genotype 1 (PrOD) and Genotype 4 (PrO) HCV infection

- **Class & Mechanism**
  - Ombitasvir (ABT-267): NS5A inhibitor
  - Paritaprevir (ABT-450): NS3/4A serine protease inhibitor
  - Ritonavir: HIV protease inhibitor used as pharmacologic booster
  - Dasabuvir (ABT-333): Non-nucleoside NS5B polymerase inhibitor

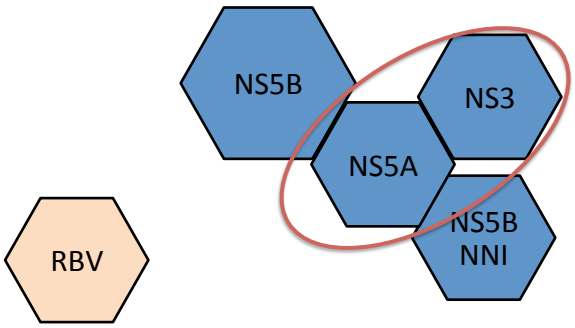
- **Dose**: 2 tablets Ombitasvir-Paritaprevir-Ritonavir(fixed dose 12.5/75/50 mg) once daily (am) with food plus Dasabuvir (250mg) 1 tablet twice daily with food
- **DI:** ++++
- **Adverse Effects (AE)**: fatigue, pruritus, and insomnia



Paritaprevir/ritonavir-Ombitasvir & Dasabuvir (PrOD) Clinical Trial Summary

STUDY	PATIENTS	REGIMEN	SVR12
PEARL-II (12 wks), Open label	GT1b, TE N=179	3D+ RBV	97% (85/88)
		3D	100% (91/91)
PEARL-III (12 wks), Double blind	GT1b, TN N=419	3D + RBV	99% (209/210)
		3D	99% (207/209)
PEARL-IV (12 wks), Double blind	GT1a, TN N=305	3D + RBV	97% (97/100)
		3D	90% (185/205)
TURQUOISE-II (12 & 24 wks) Open label Phase III	GT1, TN & TE Compensated Cirrhosis N=380	3D+ RBV 12 wks	92% (191/208)
		3D + RBV 24wks	96% (165/172)
SAPPHIRE-I (12 wks)	GT1, TN N=631	3D + RBV	96% (455/473)
SAPPHIRE-II (12 wks)	GT1, TE N=394	3D + RBV	96% (286/297)

Zepatier®
Grazoprevir(NS3/4A)/Elbasvir(NS5A)



Grazoprevir/Elbasvir (Zepatier®)

- **Approval Status:**
  - Health Canada on Jan 19, 2016
  - FDA on Jan 28, 2016
- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotypes 1 or 4
- **Class & Mechanism**
  - Elbasvir: HCV NS5A inhibitor
  - Grazoprevir: HCV NS3/4A inhibitor
- **Dosing:** Elbasvir-Grazoprevir (fixed dose 50 mg/100 mg) One tablet orally once daily, with or without food
- **DI:** Elbasvir and grazoprevir are substrates of CYP3A and P-gp
  - Co-administration of moderate and strong CYP3A inducers and inhibitors are contraindicated
  - Grazoprevir is a substrate of OATP1B1/3 and a weak CYP3A inhibitor
- **Adverse Effects(AE):**
  - Fatigue, headache, and nausea
  - Increase in ALT > 5x normal in 1% of subjects

Grazoprevir/Elbasvir Clinical Trials

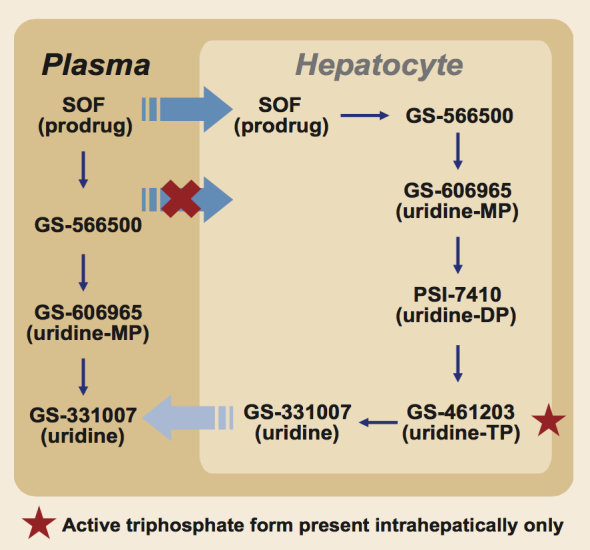
STUDY	PATIENTS	REGIMEN	SVR12
C-EDGE TN	GT 1, 4, 6 TN 22% cirrhotic	GZR/EBV 12 weeks	95%
C-EDGE TE	GT 1, 4, 6 TE 35% cirrhotic	GZR/EBV ± RBV 12 or 16 WEEKS	92-97%
C-SALVAGE	GT 1 PI experienced 43% cirrhotics	GZR/EBV + RBV 12 weeks	96%
C-WORTHY	GT 1 Cohort 1: TN Cirrhotics Cohort 2: TE (null responders) 35% cirrhotics	GZR/EBV ± RBV 12 or 16 WEEKS	90-100%

HCV THERAPY IN ADVANCED CKD

Dosing Recommendation in Renal Dysfunction

Drug	Elimination	Recommendation per package insert
Simeprevir	Hepatic (Urine <1%)	Not if CrCl < 15 ml/min
Sofosbuvir	Urine 81%	Not if CrCl < 30 ml/min
Ledipasvir	Hepatic (Urine 1%)	Unknown
Daclatasvir	Hepatic (Urine 7%)	Not required (no studies available)
Paritaprevir/ritonavir-Ombitasvir + Dasabuvir	Hepatic (Urine <11%)	Not required
Grazoprevir/ Elbasvir	Hepatic (Urine <1%)	Not required

Sofosbuvir's PK



- Only SOF can enter hepatocytes and be converted to active TP (GS-461203)
- Sofosbuvir is eliminated renally following metabolism to its nucleoside form GS-331007

Gene, et al. AASLD 2014, Poster 966

Single-Dose Sofosbuvir 400 mg in Renally Impaired Patients Without HCV*

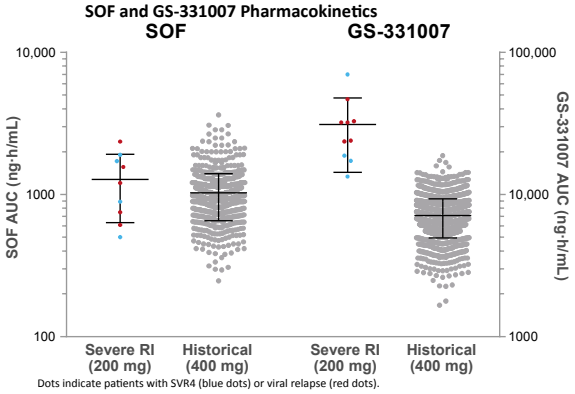
	Fold Exposure vs Patients With Normal Renal Function	
	SOF	GS-331007
Severe renal impairment	2.7	5.5
On dialysis	1.2–1.6	14–22

*Phase 1 study.[2]

Gene, et al. AASLD 2014, Poster 966

SOF 200mg + RBV in Patients with Severe Renal Impairment

- Non-cirrhotic, 7/10 TN



- Comparable SOF and ~ 4-fold higher GS-331007 exposures compared with historical HCV-infected population

Adverse Events	SOF 200 mg + RBV N=10
Anemia	5
Headache	4
Pruritus	3
Rash	3
Muscle spasms	2
Hypoesthesia	2
Insomnia	2
Irritability	2

- **SVR12: 40%**
- **SOF 200mg daily is an inadequate dosage**

Gane, AASLD, 2014, Poster #966

HCV TARGET: Real-World Analysis of SOF Regimens in Pts With Renal Dysfunction

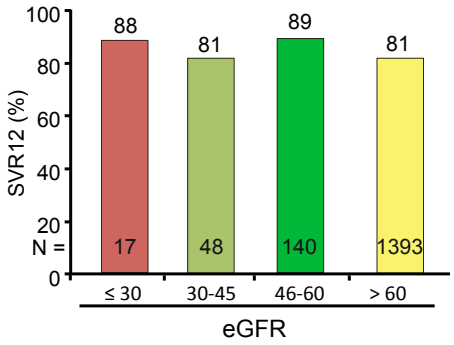
- Ongoing prospective observational cohort study
- 39 academic centers and 13 community centers in US, Germany, Israel, Canada
- Analysis evaluated safety, efficacy of sofosbuvir-containing regimens by BL renal function in 1893 sequentially enrolled pts

Baseline Characteristic	eGFR ≤ 30 (n = 19)	eGFR 31-45 (n = 63)	eGFR 46-60 (n = 168)	eGFR > 60 (n = 1643)
Presence of cirrhosis, n (%)	8 (42)	43 (68)	95 (57)	844 (51)
▪ History of decompensation	6 (32)	30 (48)	55 (33)	380 (23)
▪ MELD ≥ 10	5 (26)	26 (41)	33 (20)	227 (14)
HCC, n (%)	1 (5)	16 (25)	34 (20)	160 (10)
Liver Transplant	7 (37)	34 (54)	57 (34)	136 (8)
Kidney Transplant	3 (16)	5 (8)	9 (5)	12 (1)
Hgb (g/dL)	11.8 (8.4-17)	12.4 (8.1-17)	13.5 (9-19)	14.2 (7.3-19)
EPO at Baseline	3 (16)	3 (5)	1 (1)	1 (0)

Saxena V, et al. EASL 2015. Abstract LP08

HCV TARGET: SVR12 With SOF Regimens by Baseline *eGFR*

- Sofosbuvir + simeprevir most common regimen used
- Overall SVR12 rates high and similar (> 80%) across renal function strata in pts with known treatment outcome



- **SOF + PEG-IFN/R**
- **SOF + RBV**
- **SOF + SMV**
- **SOF + SMV + RBV**

Saxena V, et al. EASL 2015. Abstract LP08

Safety Outcomes by Baseline GFR

Dichotomous = no (%) Continuous = mean (range)	eGFR ≤ 30 (N=17)	eGFR 30-45 (N=56)	eGFR 46-60 (N=157)	eGFR>60 (N=1,559)
Common AEs				
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)
Headache	1 (6)	9 (16)	19 (12)	274 (18)
Nausea	3 (18)	8 (14)	33 (21)	247 (16)
Anemia AE	**6 (35)**	**16 (29)**	**37 (24)**	**246 (16)**
Required Transfusion(s)	2 (12)	5 (9)	3 (2)	31 (2)
Erythropoietin Start on Treatment	1 (6)	8 (14)	14(9)	50 (3)
RBV[§]				
Reduction in RBV due to Anemia	3 (38)	8 (30)	33 (42)	185 (19)
RBV Discontinuation	0 (0)	4 (15)	1 (1)	12 (1)
Worsening Renal Function[▯]	**5 (29)**	**6 (11)**	**4 (3)**	**14 (1)**
Renal or Urinary System AEs[Φ]	**5 (29)**	**6 (11)**	**13 (8)**	**84 (5)**
Any Serious AEs	**3 (18)**	**13 (23)**	**8 (5)**	**100 (6)**
Cardiac Serious AEs	**1 (6)**	**2 (4)**	**8 (5)**	**53 (3)**
Early Treatment Discontinuation	**1 (6)**	**4 (6)**	**6 (4)**	**68 (4)**
Early Treatment Discontinuation AE	**1 (6)**	**2 (3)**	**4 (2)**	**39 (3)**
Death[§]	**1 (6)**	**0 (0)**	**2 (1)**	**10 (1)**

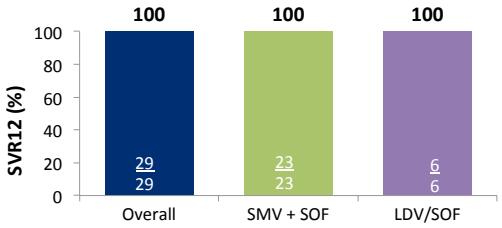
Saxena V, et al. EASL 2015. Abstract LP08

Sofosbuvir-Based, Ribavirin-Free Regimens in Patients with Chronic Hepatitis C and End-Stage Renal Disease: A Look at Safety, Tolerability and Efficacy

Interim analysis of 40 patients with HCV and ESRD from 3 US hepatology centers treated with full-dose SOF (SMV + SOF, LDV/SOF, DCV + SOF) and no RBV

SMV + SOF, 12/24 weeks (n = 29)
LDV/SOF (n = 9)
SOF + DCV (n = 2)

Baseline characteristics	N = 40
Median age, years (range)	57 (42-70)
HCV GT1a, n (%)	26 (65)
HCV RNA >800k (IU/mL)	24 (60)
On dialysis	37 (93)
Cirrhosis (F4)	21 (53)
Treatment-experienced†	10 (25)



Safety, n %	N = 40
Nausea	4 (10)
Insomnia	4 (10)
Headache	3 (8)
Pruritus	1 (2.5)
Anemia (≥2g/dL decrease in Hgb)	1 (2.5)
D/C of therapy	1 (2.5)

- No hepatic decompensation events
- No SOF dose adjustments

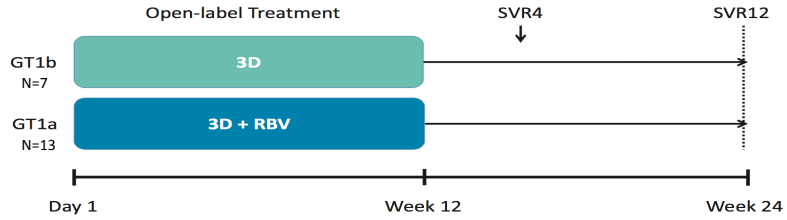
Nazario et al. EASL 2016, #SAT-164

Dosing Recommendation in Renal Dysfunction

Drug	Elimination	Recommendation per package insert
Simeprevir	Hepatic (Urine <1%)	Not if CrCl < 15 ml/min
Sofosbuvir	Urine 81%	Not if CrCl < 30 ml/min
Ledipasvir	Hepatic (Urine 1%)	Unknown
Daclatasvir	Hepatic (Urine 7%)	Not required (no studies available)
Paritaprevir/ritonavir-Ombitasvir + Dasabuvir	Hepatic (Urine <11%)	Not required
Grazoprevir/ Elbasvir	Hepatic (Urine <1%)	Not required

RUBY-1: 3D± RBV in Tx-naïve, Noncirrhotic GT1 Pts With CKD

- Interim analysis of multicenter, open-label phase IIIb study

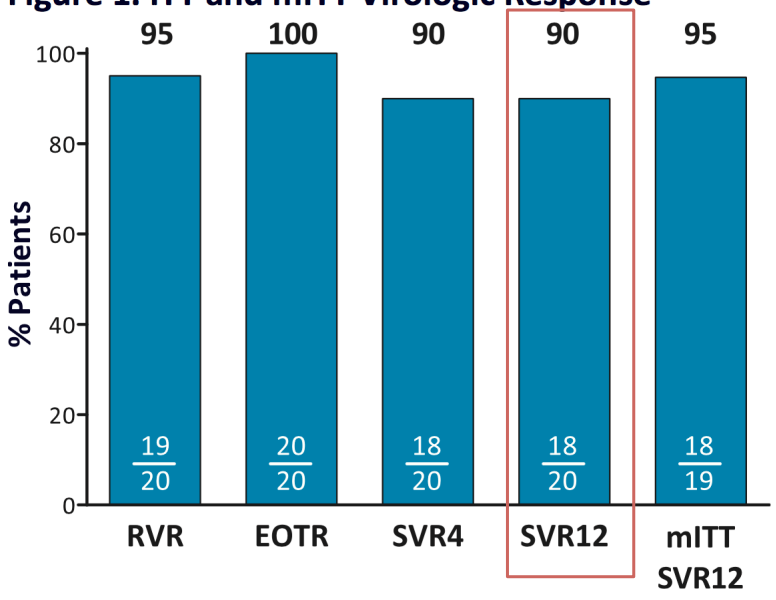


- Key baseline characteristics
  - F2 fibrosis: 30% F3 fibrosis: 20% F0-1: 50%
  - CKD stage 4 (*eGFR* 15-30): 35%
  - CKD stage 5 (*eGFR* < 15): 65% on hemodialysis

RBV dosed 4 hrs before hemodialysis in hemodialysis pts; wkly Hb assessment in Mo 1 and then Wks 6, 8, 12; RBV suspended in pts with > 2 g/dL decline in Hb in < 4 wks or Hb < 10 g/dL; RBV dosing resumed at clinician's discretion if Hb normalized.

Pockros PJ, et al. EASL 2015. Abstract L01.

Figure 1. ITT and mITT Virologic Response



Adapted from Pockros PJ, et al. AASLD 2015. Abstract 1039

Treatment-emergent AEs and Laboratory Abnormalities

Event, n (%)		GT1a OBV/PTV/r + DSV + RBV, N=13	GT1b OBV/PTV/r + DSV, N=7
Any AE assessed as being related to DAAs		8 (62)	2 (29)
Serious AE		3 (23)	1 (14)
AE leading to study drug discontinuation		0	0
AE leading to RBV dose reduction		9 (69)	NA
Death		1 (8)	0
AEs occurring in >15% of patients overall	Anemia	9 (69)	0
	Fatigue	5 (38)	2 (29)
	Diarrhea	4 (31)	1 (14)
	Nausea	5 (38)	0
	Headache	3 (23)	0
	Peripheral edema	1 (8)	2 (29)
Hemoglobin	Grade 2 (<10–8 g/dL)	7 (54)	2 (29)
	Grade 3 (<8–6.5 g/dL)	1 (8)	0
Total Bilirubin	Grade 2 (>1.5–3 x ULN)	2 (15)	0
	Grade 3 (>3–10 x ULN)	0	0
Alanine aminotransferase	Grade 3 (>5–20 x ULN)	0	0
Aspartate aminotransferase	Grade 3 (>5–20 x ULN)	0	0

Adapted from Pockros et al , Poster 1039; AASLD , November 13-17, 2015

10

Dosing Recommendation in Renal Dysfunction

Drug	Elimination	Recommendation per package insert
Simeprevir	Hepatic (Urine <1%)	Not if CrCl < 15 ml/min
Sofosbuvir	Urine 81%	Not if CrCl < 30 ml/min
Ledipasvir	Hepatic (Urine 1%)	Unknown
Daclatasvir	Hepatic (Urine 7%)	Not required (no studies available)
Paritaprevir/ritonavir-Ombitasvir + Dasabuvir	Hepatic (Urine <11%)	Not required
Grazoprevir/ Elbasvir	Hepatic (Urine <1%)	Not required

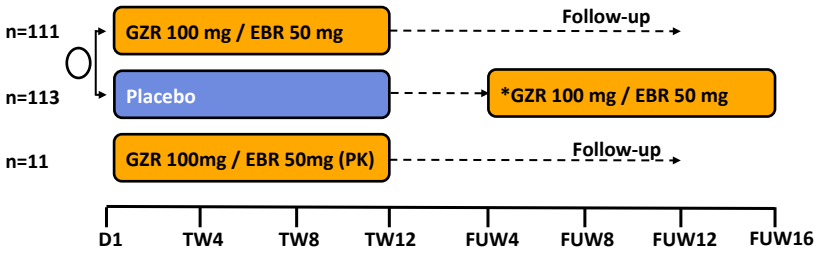
Articles

Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study

David Roth, David R Nelson, Annette Bruchfeld, AnnMarie Liapakis, Marcelo Silva, Howard Monsour Jr, Paul Martin, Stanislas Pol, Maria-Carlota Londoño, Tarek Hassanein, Philippe J Zamor, Eli Zuckerman, Shuyan Wan, Beth Jackson, Bach-Yen Nguyen, Michael Robertson, Eliav Barr, Janice Wahl, Wayne Greaves

www.thelancet.com **Published online October 6, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00349-9**

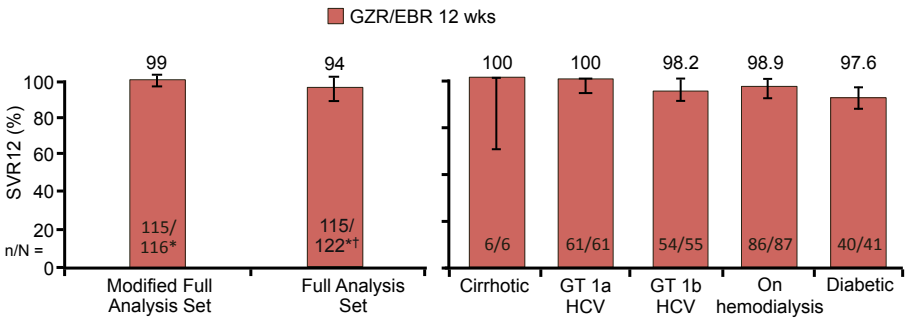
C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4 or 5 CKD



- GT 1 (52% for GT1a)
- Treatment-naive (83%) and treatment-experienced patients (17%)
- 6% had compensated cirrhosis
- 75% and 77% were on hemodialysis; 32% to 36% were diabetic
- 81% and 82% were CKD stage 5 (eGFR < 15 mL/min/1.73 m^2, or on hemodialysis); 18% and 19% were CKD stage 4 (eGFR 15-29 mL/min/1.73 m^2)

Roth D. et al. ASN 2015. LB SA-PO1100.

C-SURFER: Efficacy Results



Modified analysis set: pts in pharmacokinetic substudy and pts randomized to immediate treatment who received ≥ 1 drug dose; excludes pts who died or discontinued where cause not related to study treatment.
Full analysis set: all pts receiving ≥ 1 drug dose.
*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).

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Adverse Events

	GZR/EBR (ITG) (n = 111)	GZR/EBR (DTG) (n = 102)	Placebo (DTG) (n = 113)	Difference in % Estimate ITG vs placebo (95% CI)
AEs, n (%)	84 (75.7)	61 (59.8)	95 (84.1)	–8.3 (–18.9, 2.2)
Headache	19 (17.1)	7 (6.9)	19 (16.8)	0.3 (-9.6, 10.4)
Nausea	17 (15.3)	10 (9.8)	18 (15.9)	–0.6 (–10.3, 9.1)
Fatigue	11 (9.9)	9 (8.8)	17 (15.0)	–5.1 (–14.1, 3.7)
Insomnia	7 (6.3)	2 (2.0)	12 (10.6)	–4.3 (–12.2, 3.2)
Dizziness	6 (5.4)	5 (4.9)	18 (15.9)	–10.5 (–19.1, -2.6)
Diarrhea	6 (5.4)	5 (4.9)	15 (13.3)	–7.8 (–16.1, -0.2)
Serious AEs, n (%)	16[b] (14.4)	13[c] (12.7)	19 (16.8)	–2.4 (–12.1, 7.3)
Discon due to an AE, n (%)	0 (0)	3 (2.9)	5 (4.4)	–4.4 (10.0, -1.0)
Deaths,[d] n (%)	1 (0.9)	0 (0)	3 (2.7)	–1.8 (–6.7, 2.5)

[b]1 SAE in the DTG (placebo) was considered drug-related (elevated lipase level).
[c]1 SAE in the DTG (EBR/GZR) was considered drug-related (interstitial nephritis).
[d]1 ITG patient died of cardiac arrest and 3 DTG patients died of aortic aneurysm, pneumonia, and unknown cause.

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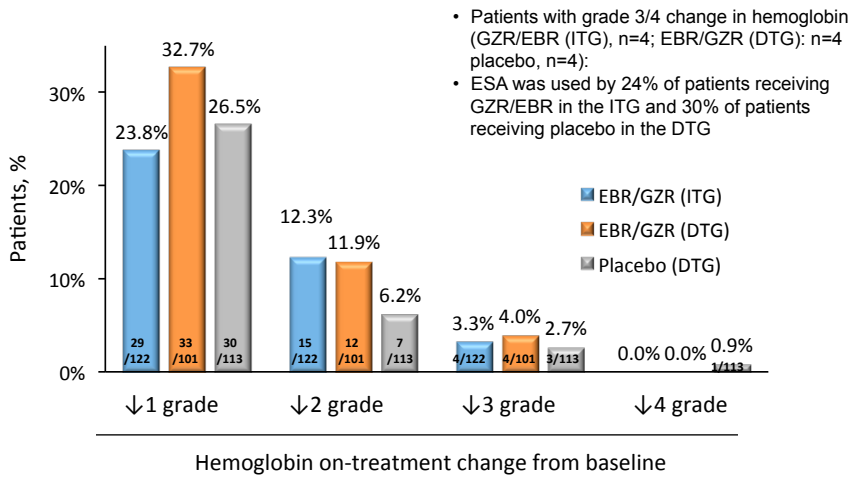
Hemoglobin: on-treatment change



ESA = erythropoietin stimulating agent
Grade 0: >10.9 g/dL; grade 1: 10.0-10.9 g/dL; grade 2: 9.0-9.9 g/dL; grade 3: 7.0-8.9 g/dL; grade 4: <7.0 g/dL.

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Drug	Main route of Elimination	Dosage in eGFR 15-29 mL/min	Dosage in HD & eGFR <15 mL/min
Grazoprevir/ Elbasvir	Hepatic (Urine <1%)	Not required (C-SURFER)	Not required (C-SURFER)
Paritaprevir/ ritonavir-Ombitasvir + Dasabuvir	Hepatic (Urine <11%)	Not required (RUBY-1) *GT1a require RBV	Not required (RUBY-1) *GT1a require RBV
Sofosbuvir	Urine 81%	Likely not required (HCV TARGET, PC, PK study underway)	More studies required (TARGET, PC, PK study underway)
Ledipasvir	Hepatic (Urine 1%)	Not required (no studies available)	Likely not required (no studies available)
Daclatasvir	Hepatic (Urine 7%)	Not required (no studies available)	Not required (no studies available)
Simeprevir	Hepatic (Urine <1%)	Not required (HCV TARGET, PC)	Not required (HCV TARGET, PC)