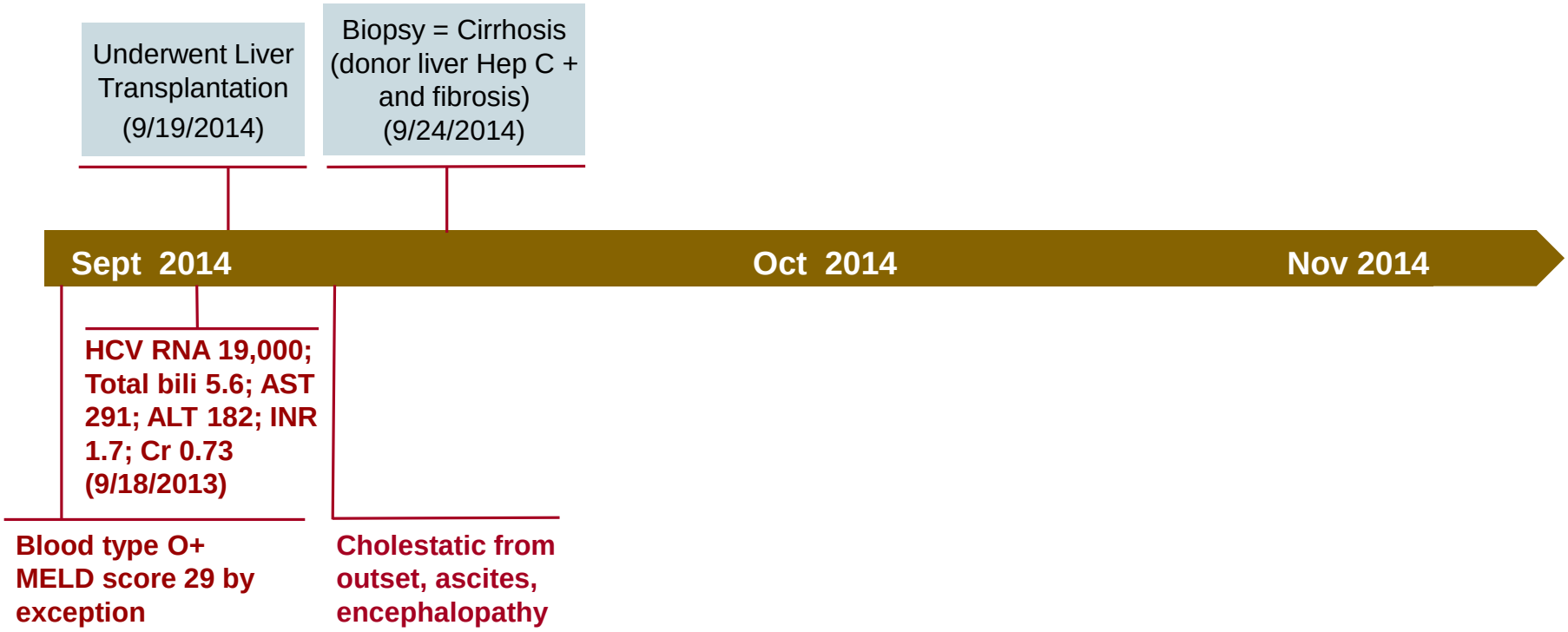
Obstacles to Treatment: Renal Disease, Ribavirin, DDIs

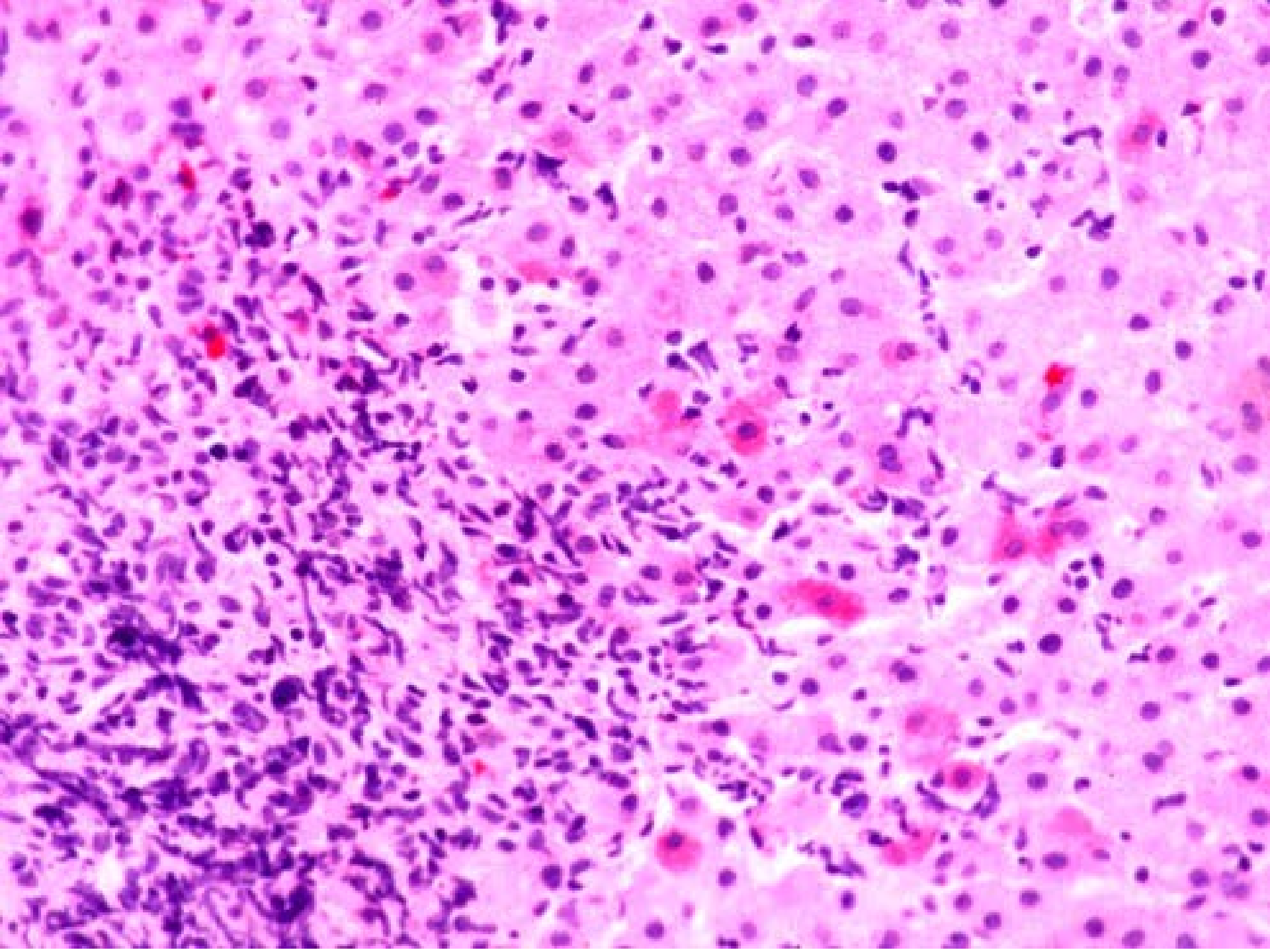
Disclosures

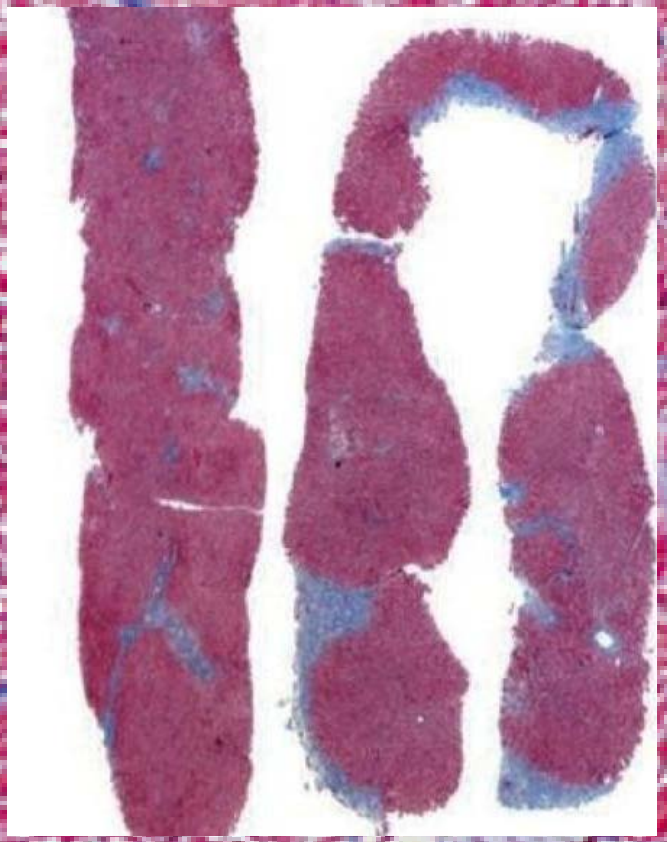
- Research Support:
  - Gilead, Novartis, Bristol Myers Squibb, Astellas, AbbVie, Merck, Janssen, Roche/Genentech
- Consulting:
  - Gilead, Novartis, Bristol Myers Squibb, Astellas, AbbVie, Merck, Janssen, Roche/Genentech

Case Presentation

- **51 yo female with cirrhosis secondary to HCV GT 1a, complicated by hepatopulmonary syndrome**

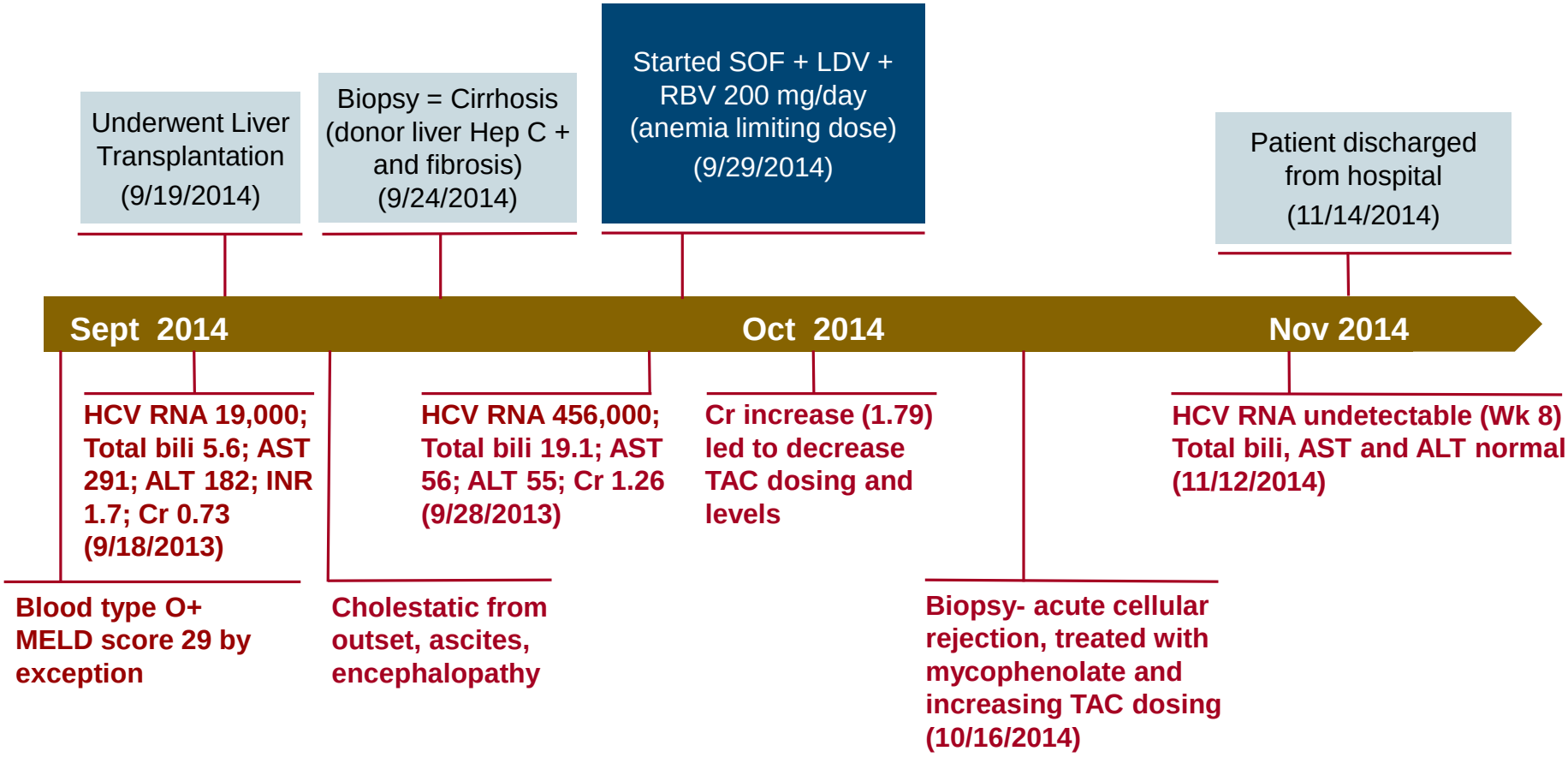




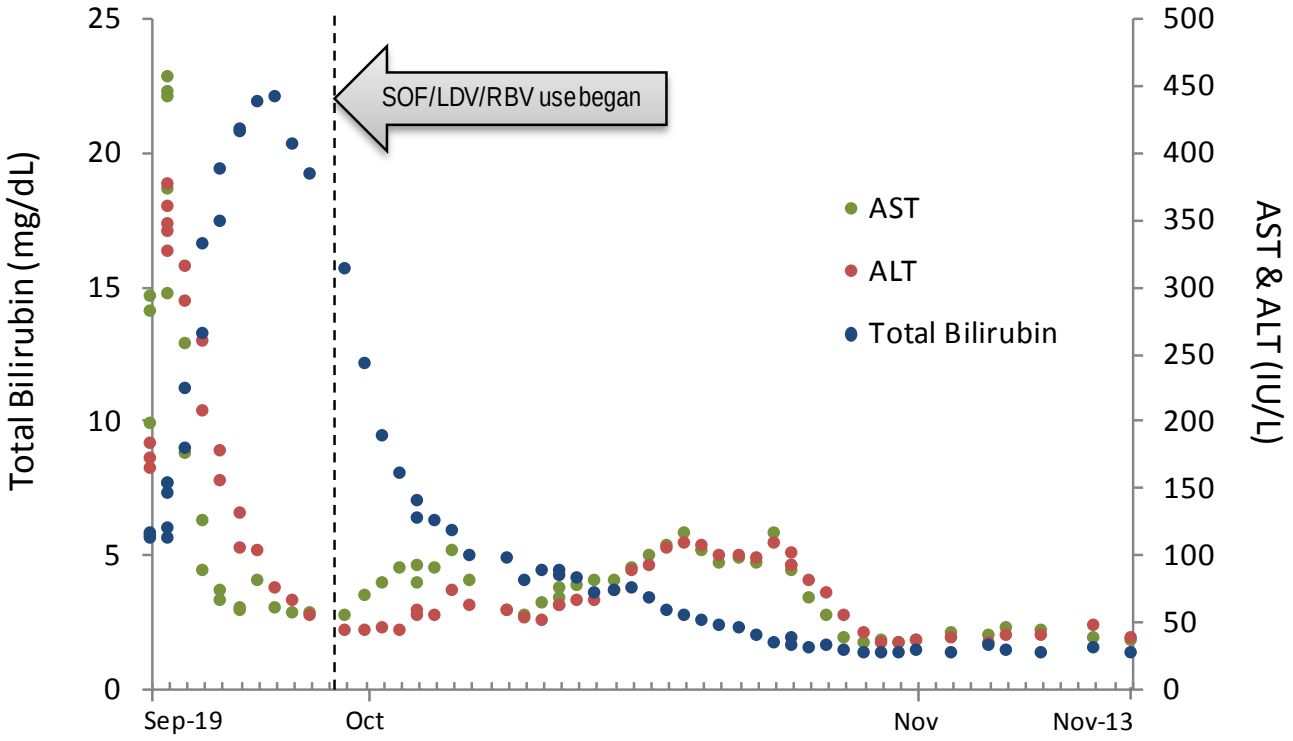


Case Presentation

- **51 yo female with cirrhosis secondary to HCV GT 1a, complicated by hepatopulmonary syndrome**



Case - continued



Rx x 12 weeks,
6 wks post EOT, ALT216 IU/L, HCV RNA 347,000 IU/ml

What happened?

Renal Disease

LDV/SOF: Metabolism

Sofosbuvir: 80% of dose excreted in urine (most as 007) - 007 $t_{1/2}$ is 27 hours

	AUC (% increase) compared to GFR >80		
	Mild	Moderate	Severe
SOF	61%	107%	171%
331007	55%	85%	451%

HD: 12-20 fold increase in 007 AUC

Ledipasvir: Primarily eliminated in feces (>70%)
Limited (<2.0%) urinary excretion
No changes in exposure with GFR <30

Cornpropst M, et al. Presented at: EASL; April 18-22, 2012; Barcelona, Spain. Abstract 1101; Kirby B, et al. Presented at: International Workshop on Clinical Pharmacology of Hepatitis Therapy; June 26-27, 2013; Cambridge, MA. Poster O22;
HARVONI (ledipasvir and sofosbuvir) tablets [package insert]. Foster City, CA: Gilead Sciences; October 2014. SOVALDI (sofosbuvir) tablets [package insert]. Foster City, CA: Gilead Sciences; December 2013.

3D Regimen: Metabolism

- All components: hepatic metabolism
  - <2% excreted in urine

	AUC (% increase) when GFR <30			
	PAR	RTV	OMB	DAS
Cmax	↔	66%	↔	↔
AUC	45%	114%	↔	50%

OMB:Ombitasvir, PAR: Paritaprevir, RTV: Ritonavir, DAS: Dasabuvir

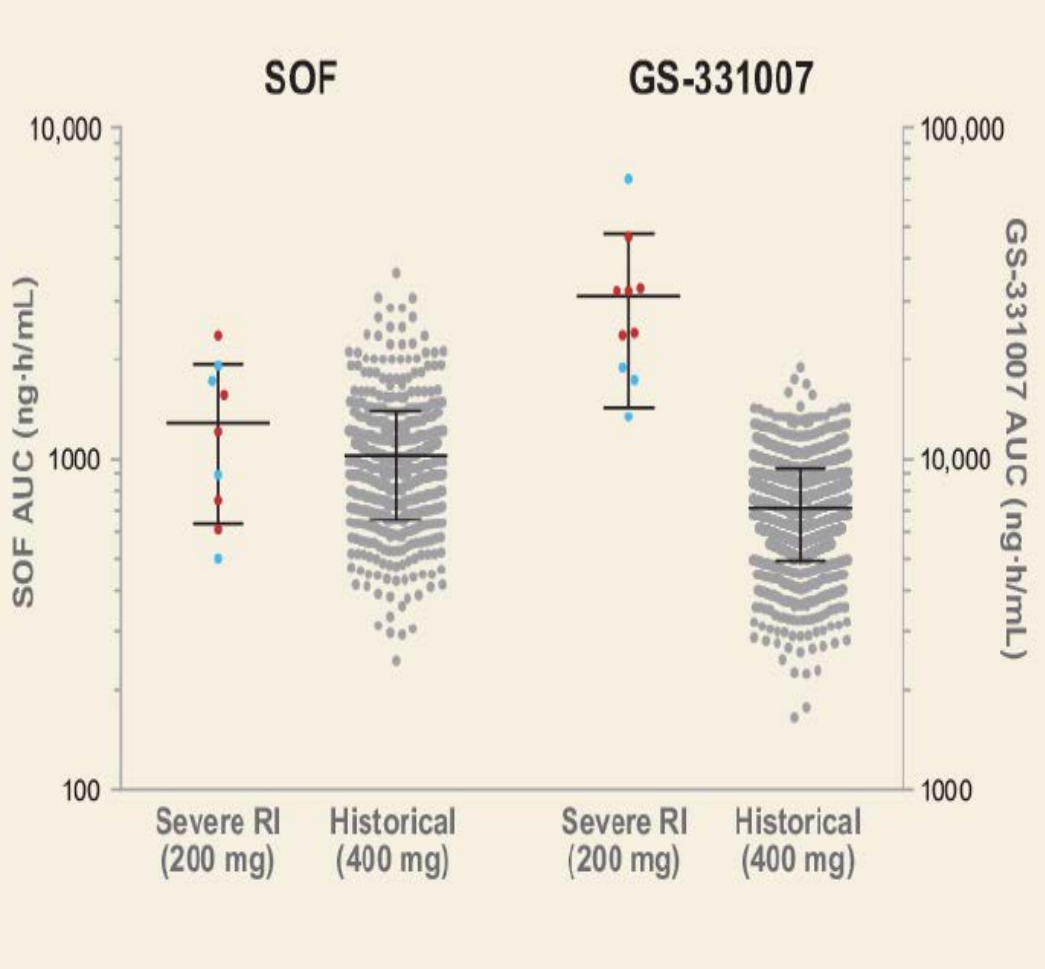
VIEKIRA PAK (ombitasvir, paritaprevir and ritonavir + dasabuvir) tablets [package insert]. North Chicago, IL: AbbVie Inc.; December 2014.

What Do the Package Labels Say About Renal Impairment?

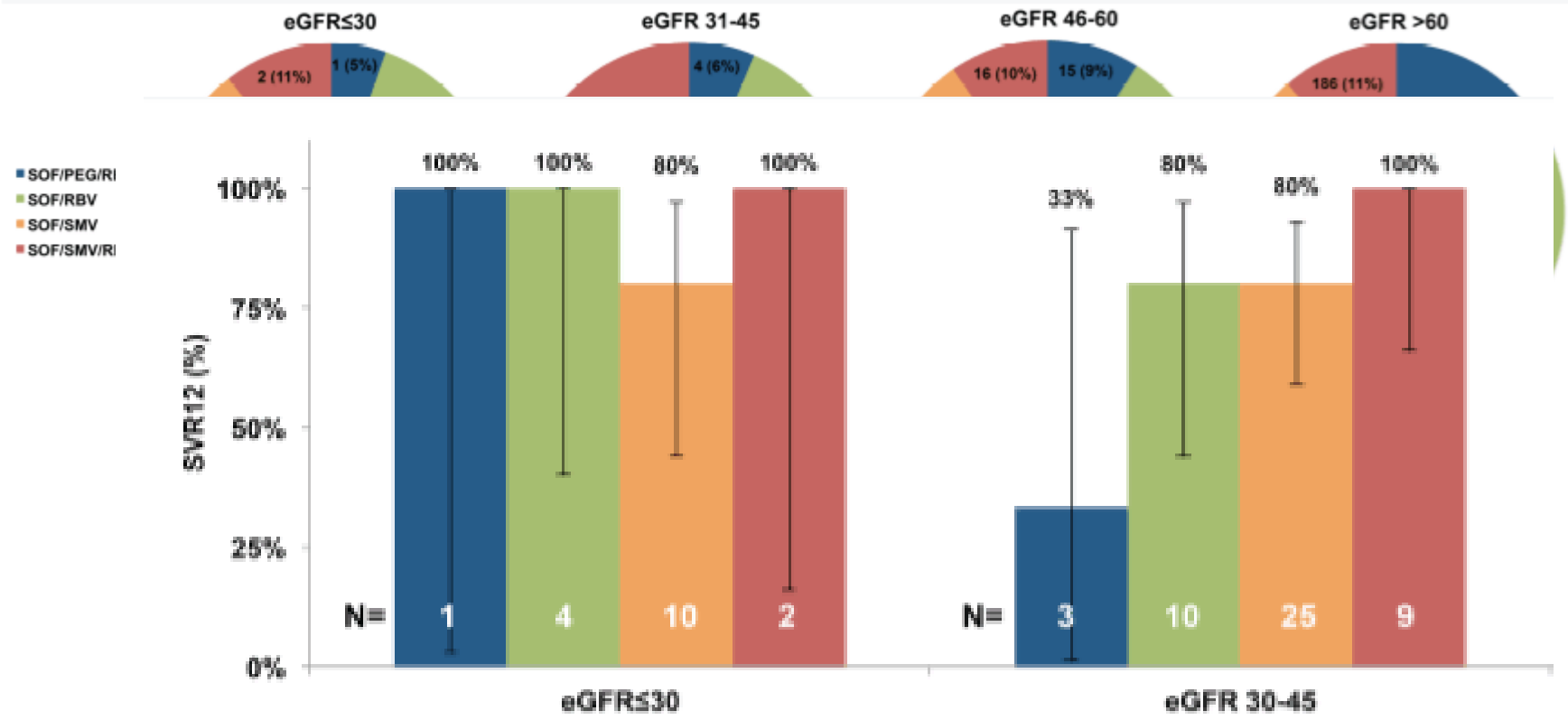
Drug/Regimen	Label Language
SOF	No dose adjustment for mild-moderate renal disease. No dose recommendation can be given for eGFR <30 mL/min/1.73m^2 or ESRD. Accumulation of SOF metabolite (GS-331007) up to 20x expected. Safety and efficacy not established.
LDV/SOF	Same as SOF alone.
SMV	No dose adjustment necessary for mild, moderate, or severe renal impairment. Not studied in patients with GFR <30 or on dialysis.
3D + RBV	No dose adjustment necessary for mild, moderate, or severe renal impairment. Not studied in patients on dialysis.
RBV	Moderate (30-50 mL/min): 200 mg/400 mg alternating QOD Severe or HD (<30 mL/min): 200 mg QD
GRZ/EBV	No dose adjustment necessary for mild, moderate, or severe renal impairment.

See individual prescribing information at
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

SOF and 007 Plasma Exposures



SOF-based Treatment in Renal Failure Outcomes By Baseline eGFR

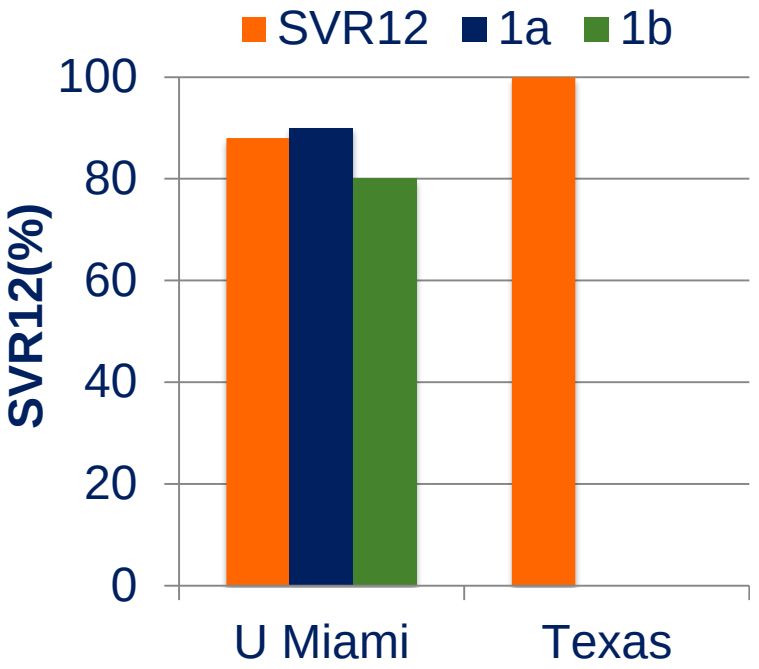


Worsening Renal Function[♣]	5 (29)	6 (11)	4 (3)	14 (1)
Renal or Urinary System AEs[♦]	5 (29)	6 (11)	13 (8)	84 (5)
Any Serious AEs	3 (18)	13 (23)	8 (5)	100 (6)
Cardiac Serious AEs	1 (6)	2 (4)	8 (5)	53 (3)
Early Treatment Discontinuation	1 (6)	4 (6)	6 (4)	68 (4)
Early Treatment Discontinuation AE	1 (6)	2 (3)	4 (2)	39 (3)
Death[§]	1 (6)	0 (0)	2 (1)	10 (1)

Saxena et al., Liver Int. 2016 Feb 29. [Epub ahead of print].

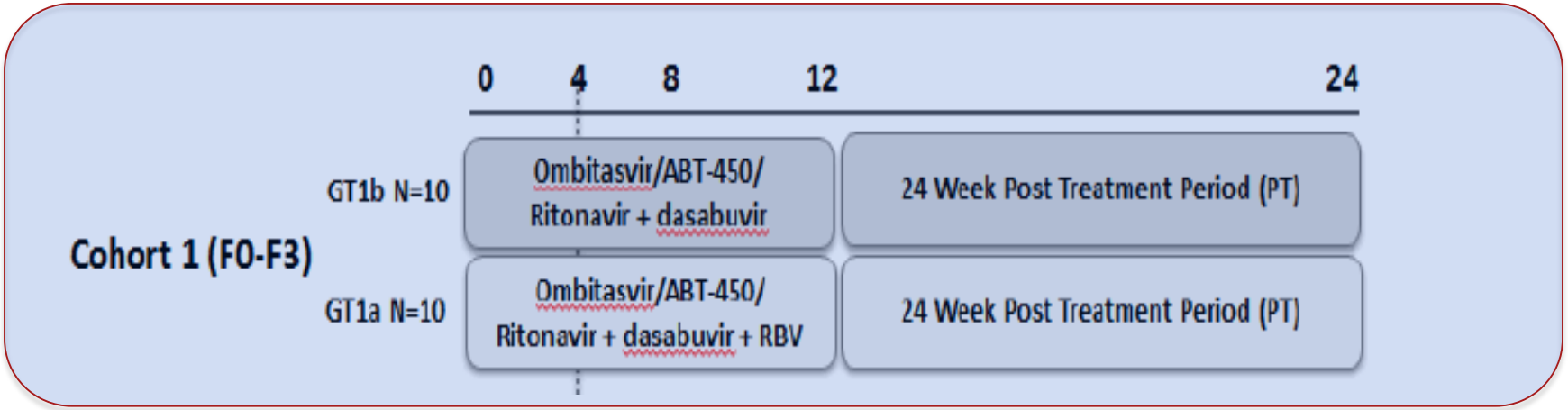
Label Be Damned – Real-world Experience with SOF/SMV in ESRD

- Miami: 16 patients – GFR <15 or HD
  - 42% naïve, 58% cirrhotic
  - SOF 200 mg QD +
    SMV 150 mg QD; no RBV
    - 3 patients: SOF 400 mg QOD with SMV
- Texas: 11 patients– GFR <30 or HD
  - 82% naïve, 47% cirrhosis
  - SOF 400 mg QD +
    SMV 150 mg QD; no RBV
  - 88% on HD



Czul F, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Poster P0878.
Nazario HE, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Poster P0802.

3D + RBV in Treatment-naïve Patients with ESRD



20 patients enrolled; SVR4 data on 10

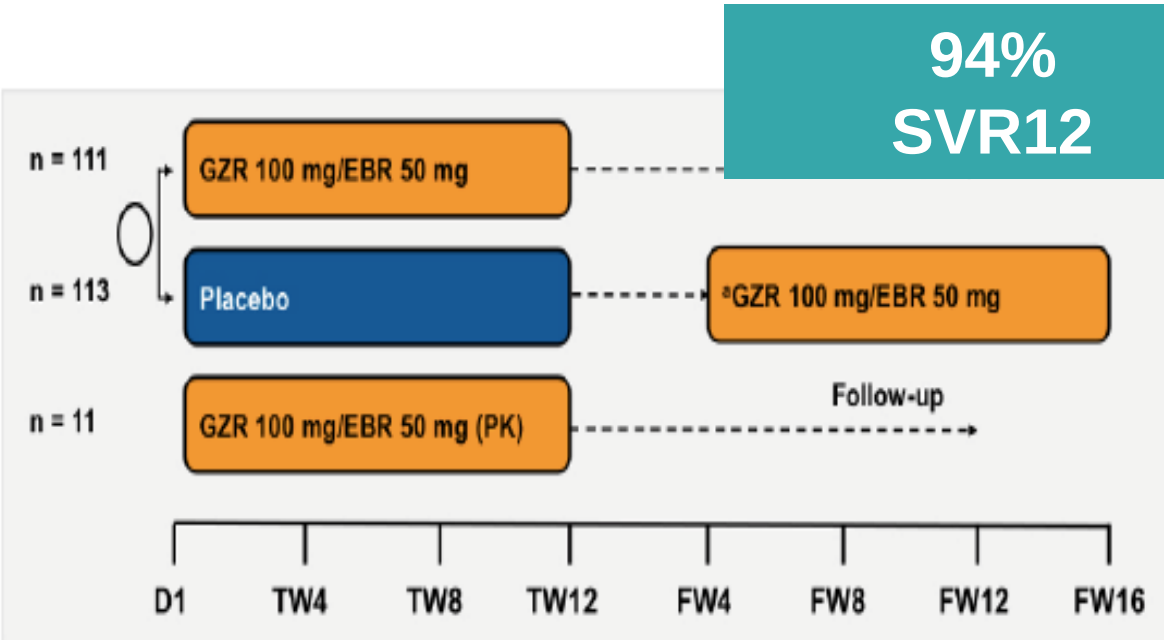
100% SVR4

8/13 genotype 1a with RBV dose interruption

Pockros PJ, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Oral Presentation LO1.

Grazoprevir/Elbasvir in ESRD

- GZR/EBR: both <1% renal elimination
  - No dose adjustment needed

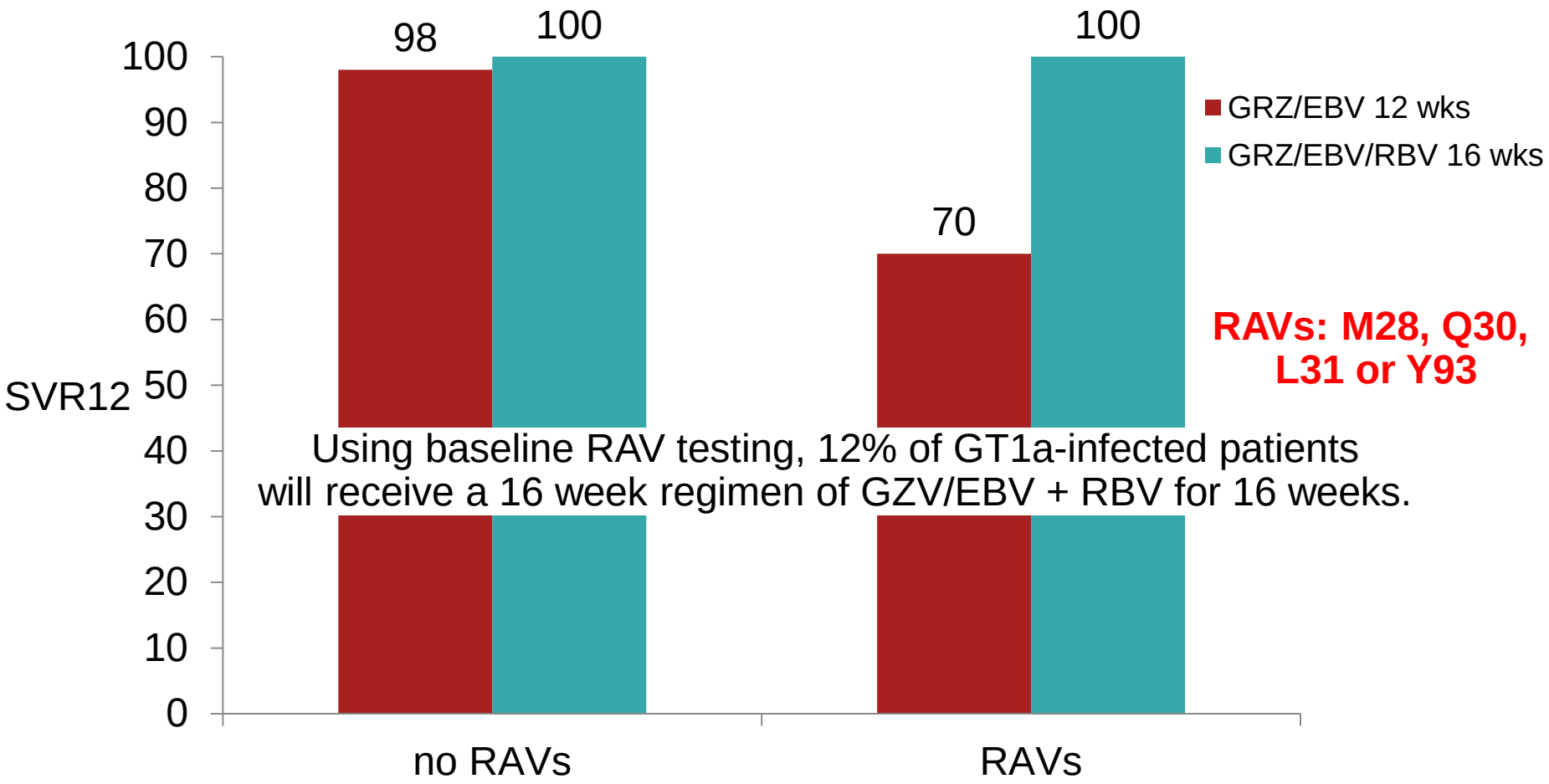


- 81% CKD stage 5
- (GFR <15 or HD)

Roth D, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Poster LP02.

Ribavirin

Efficacy of GZV/ELB +/- RBV in Patients with and without NS5A RAVs at Baseline in GT 1a

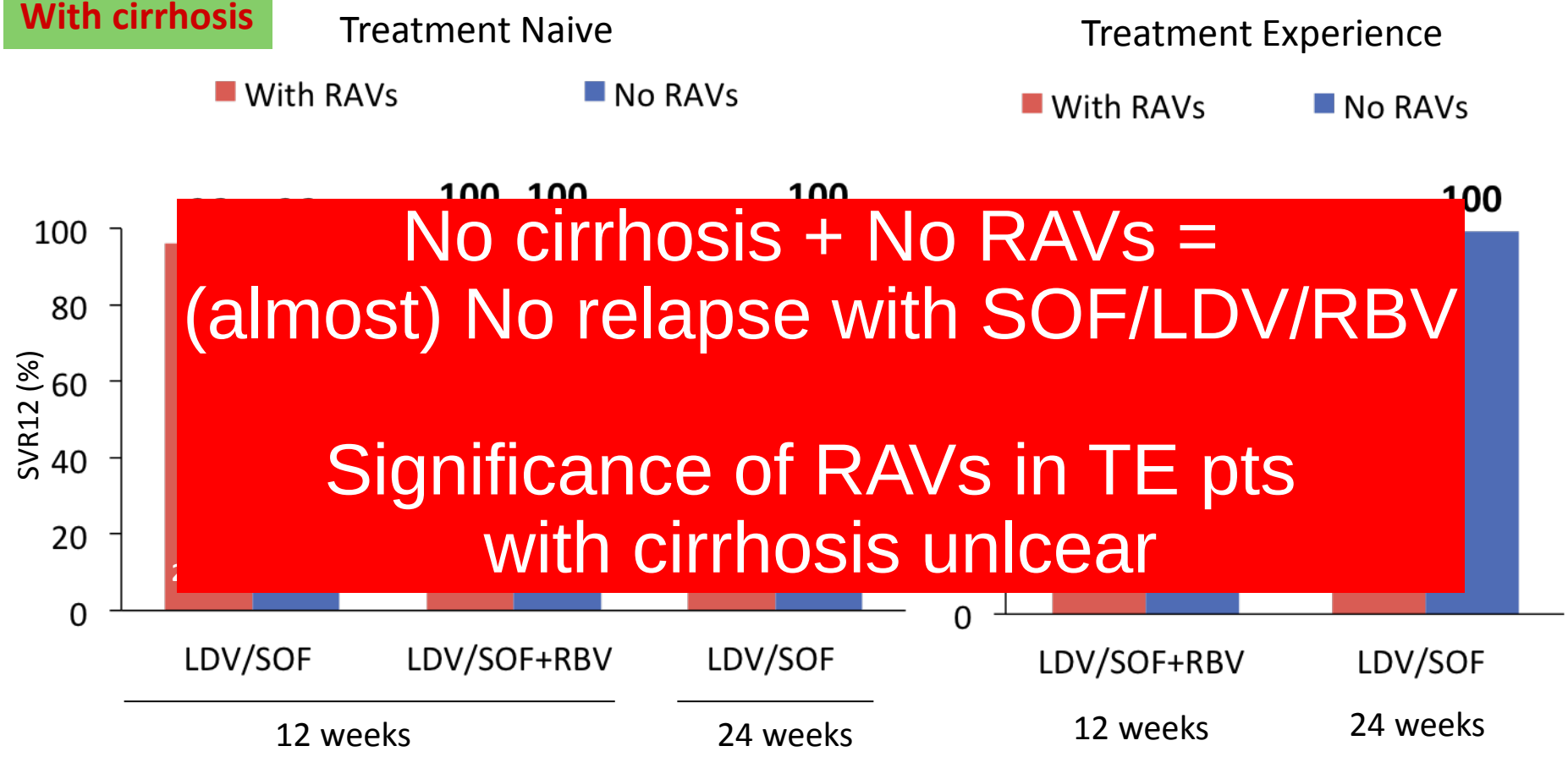


C-WORTHY study, treatment-naïve cirrhotics and prior PR null responders ±cirrhosis) (*Hepatology 62(Suppl. S1):2A-1378A 2015*) and Thompson et al. (*Hepatology 62(Suppl. S1)):556A-557A Abstract 703 2015*), Lancet.2015;385(9973:1075-1081).

Efficacy of LDV-SOF in Patients with and without NS5A RAVs at Baseline

Zeuzem S, Abstract 91

With cirrhosis

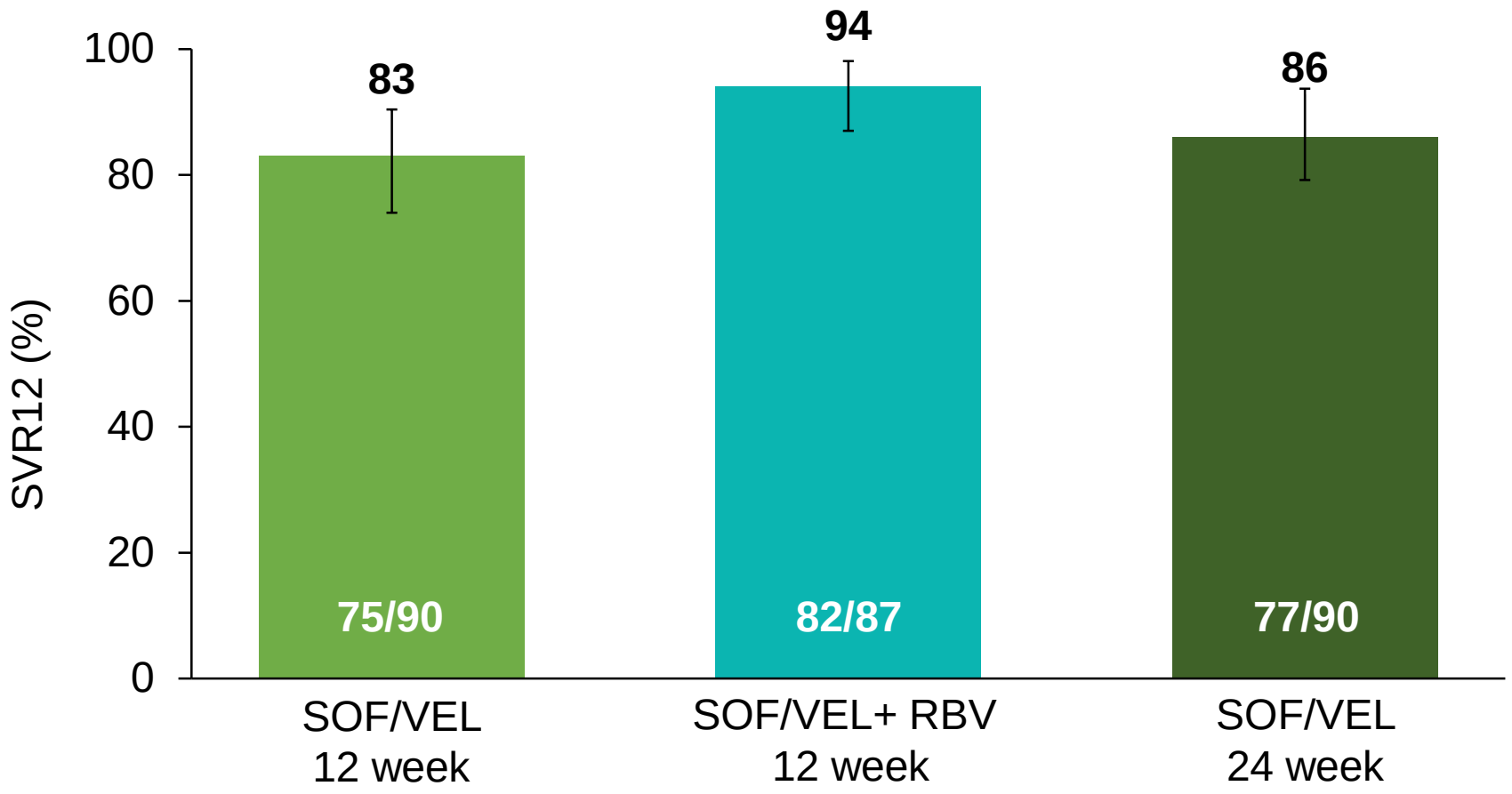


No cirrhosis + No RAVs =
(almost) No relapse with SOF/LDV/RBV

Significance of RAVs in TE pts
with cirrhosis unlcear

Studies included for analysis:
LDV/SOF 12 Wks: GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (ELECTRON-2), GS-US-337-0131(China), GS-US-337-1406; **LDV/SOF+RBV 12 Wks**: GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0122 (ELECTRON-2); **LDV/SOF 24 Wks**: GS-US-337-0102 (ION-1), GS-US-334-1274 (Bleeding Disorder)

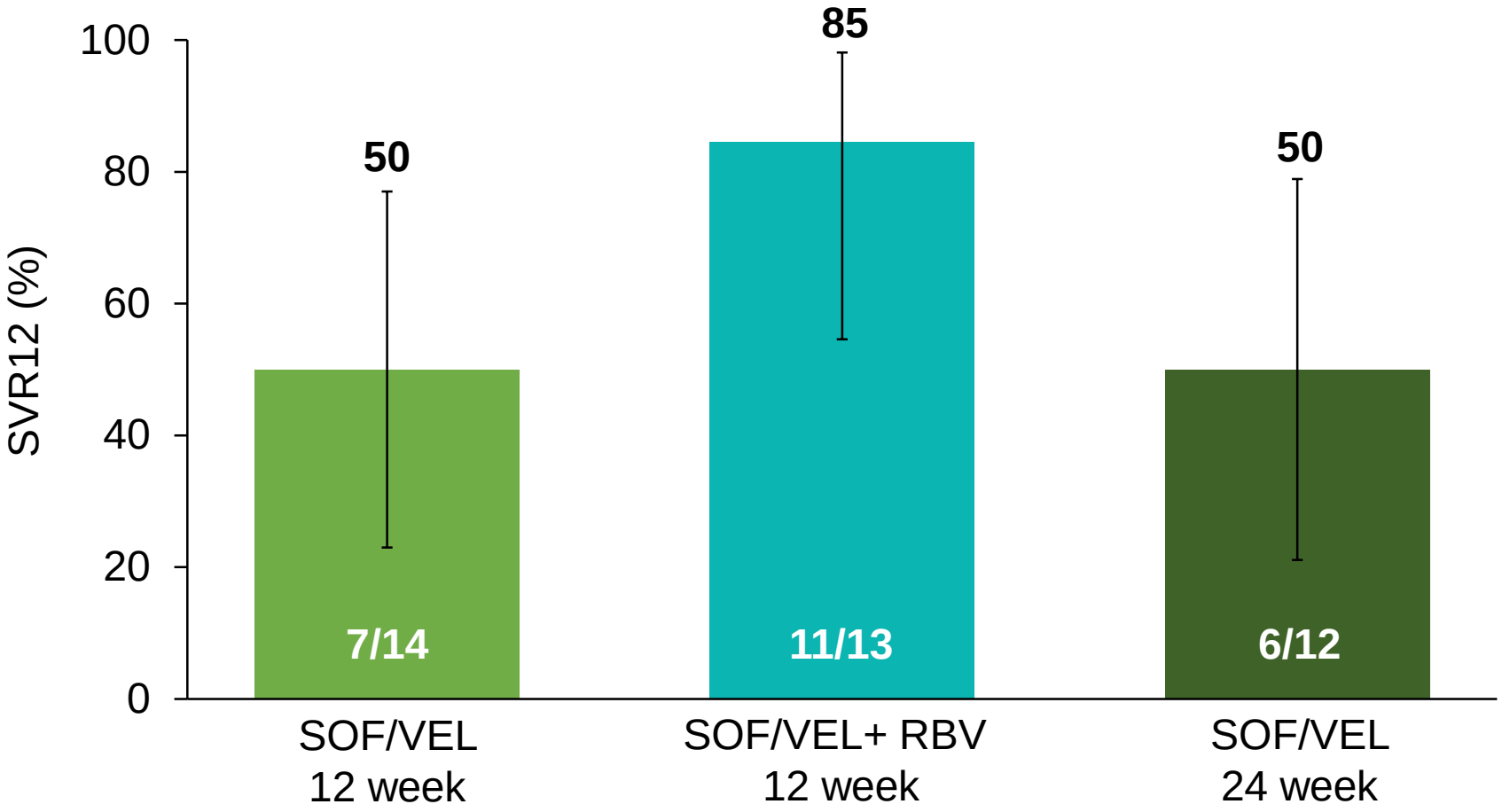
SOF + Velpatasvir
Overall SVR12 in Genotype 1 CPT B/C



P-value < 0.001 for comparison of SVR12 rate to 1% for each treatment group
Error bars represent 95% confidence intervals.

N Engl J Med. 2015 2015; 373:2618-2628

SOF + Velpatasvir
Overall SVR12 in Genotype 3 CPT B/C



Error bars represent 95% confidence intervals.

N Engl J Med. 2015 2015; 373:2618-2628

Renal Failure

- Posttransplant conundrum:
  - SOF is not recommended if eGFR </=30mls/min
  - GRZ/EBV not recommended posttransplant (DDIs)

- Use SOF-based Rx if eGFR >30 mls/min

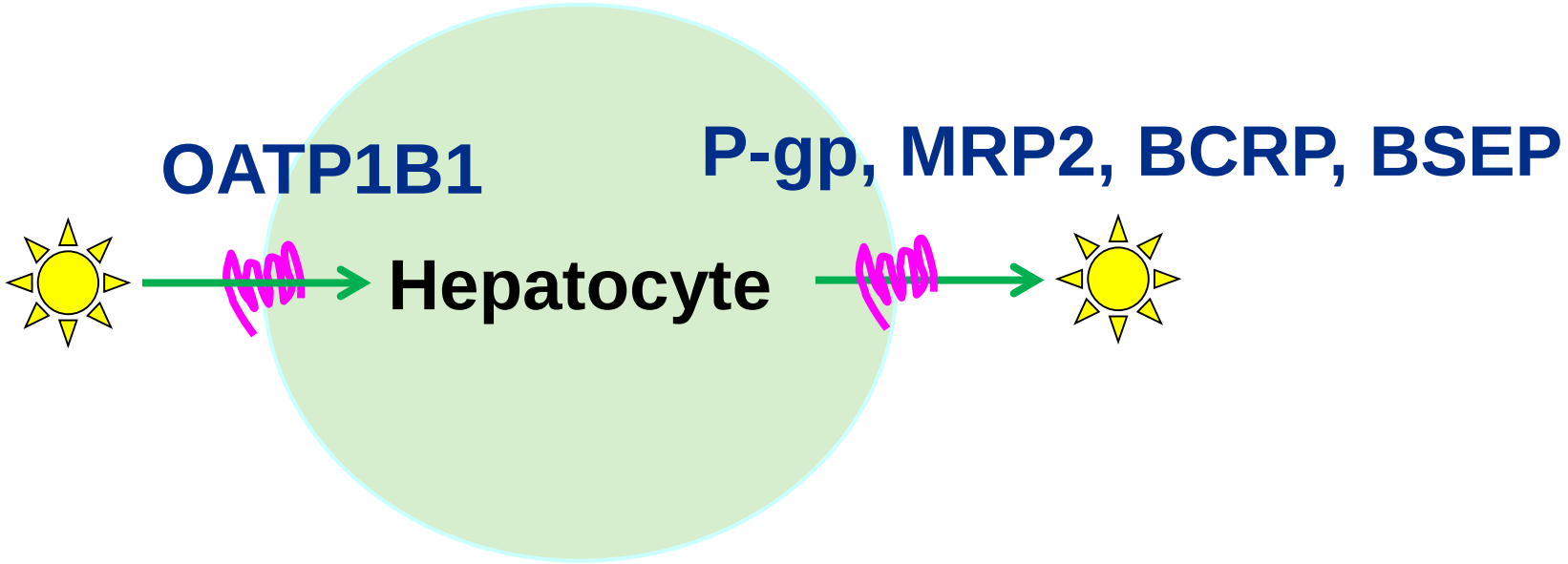
- Renally dose RBV
  - GFR 30-50 mL/min: 200 mg/400 mg alternating QOD
  - GFR <30 mL/min: 200 mg QD

- SOF vs. GRZ vs. 3D if eGFR </=30 mls/min?

DDIs

Transporter-mediated Interactions

Like enzymes, transporter expression can be induced and transporter function can be inhibited.



DAAs as Victims

Medication	Daclatasvir		Ledipasvir		Sofosbuvir		Simeprevir	
	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
Cyclosporine	↑ 4%	↑ 40%	ND	ND	↑ 154%	↑ 353%	↑ 374%	↑ 481%
Tacrolimus	↑ 7%	↑ 5%	ND	ND	↓ 3%	↑ 13%	↑ 79%	85%

Dick TB, et al. *Hepatology.* 2015.

DAAs as Culprits

Medication	Cyclosporine		Tacrolimus		Sirolimus		Everolimus	
	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
Ribavirin	⇔	⇔	⇔	⇔	⇔	⇔	⇔	⇔
Ledipasvir	⇔	⇔	ND	ND	ND	ND	ND	ND
Sofosbuvir	⇔	⇔	27%	9%	ND	ND	ND	ND
Simeprevir	16%	19%	24%	17%	ND	ND	ND	ND
Daclatasvir	4%	3%	5%	⇔	ND	ND	ND	ND
3D Regimen	1%	↑ 482%	↑ 299%	↑ 5613%	Expected increase in both Cmax and AUC.		Expected increase in both Cmax and AUC.	

HCV infection inhibits cytochrome P450 through direct and indirect mechanisms. SVR leads to lower CNI levels and risk of ACR.

Dick TB, et al. *Hepatology.* 2015. [Epub ahead of print]

DDI Exclusion Criteria for Ombitasvir, Paritaprevir and Ritonavir + Dasabuvir – Phase 3 Medications Contraindicated

Not all medications contraindicated with ritonavir and ribavirin are listed below. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications

Drug Class	Drug
Antiarrhythmic	Dronedarone, Amiodarone, Propafenone, Quinidine
Anti-asthmatic	Montelukast, Salmeterol
Anticonvulsant	Carbamazepine, Phenobarbital, Phenytoin
Antidepressant	Nefazodone
Antidiabetic	Pioglitazone, Rosiglitazone, Troglitazone
Antifungal	Itraconazole, Ketoconazole, Voriconazole
Antihistamine	Astemizole, Terfenadine
Antihyperlipidemic	Lovastatin, Gemfibrozil, Simvastatin
Antihypertensive	Bepridil, Eplerenone
Anti-infective	Clarithromycin, Fusidic Acid, Telithromycin, Trimethoprim, Troleandomycin
Antimycobacterial	Rifabutin, rifampin
Narcotic analgesic	Methadone, Buprenorphine
Sedative/hypnotic	Midazolam, Triazolam

Drug Class	Drug
Other	Alfuzosin (alpha adrenoreceptor antagonist) Cisapride (GI motility agent) Bosentan (endothelin receptor antagonist) Conivaptan (cardiovascular agent) Efavirenz (HIV) Eletriptan (selective serotonin receptor agonist) Ergot derivatives (neurologics) Everolimus (anticancer) Quercetin (anti-inflammatory) Mifepristone (steroid) Modafinil (stimulant) Pimozide (antipsychotic) St. John's Wort (herbal product)

1. Citeline.com (TrialTrove). Accessed February 19, 2014.

Effect of Acid Reducing Agents on LDV/SOF PK

H2-Receptor Antagonists (H2-RA)

Parameter		Geometric Mean			%Geometric Mean Ratio (90% CI)	
		LDV/SOF	+FAM	+FAM (12-hr stagger)	LDV/SOF+FAM Simultaneous/ LDV/SOF	LDV/SOF+FAM Stagger/ LDV/SOF
LDV	C_{max}	212	170	176	80.3 (69.1, 93.3)	82.9 (69.0, 99.7)
	AUC	7120	6360	6980	89.3 (75.5, 106)	98.1 (80.1, 120)
SOF	C_{max}	1430	1640	1440	115 (87.7, 150)	100 (76.4, 132)
	AUC	2340	2610	2230	111 (99.5, 124)	95.0 (82.4, 110)
GS-331007	C_{max}	648	683	733	106 (97.4, 114)	113 (107, 120)
	AUC	13300	14100	14100	106 (102, 111)	106 (101, 112)

- LDV/SOF may be administered H2RA at a dose not exceeding famotidine 40 mg twice daily

AUC_{inf} (ng*hr/ml)=area under the plasma concentration versus time curve extrapolated to infinite time; CI=confidence interval; C_{max}(ng/ml)=maximum observed plasma concentration of drug; FAM: famotidine 40 mg

Effect of Acid Reducing Agents on LDV/SOF PK

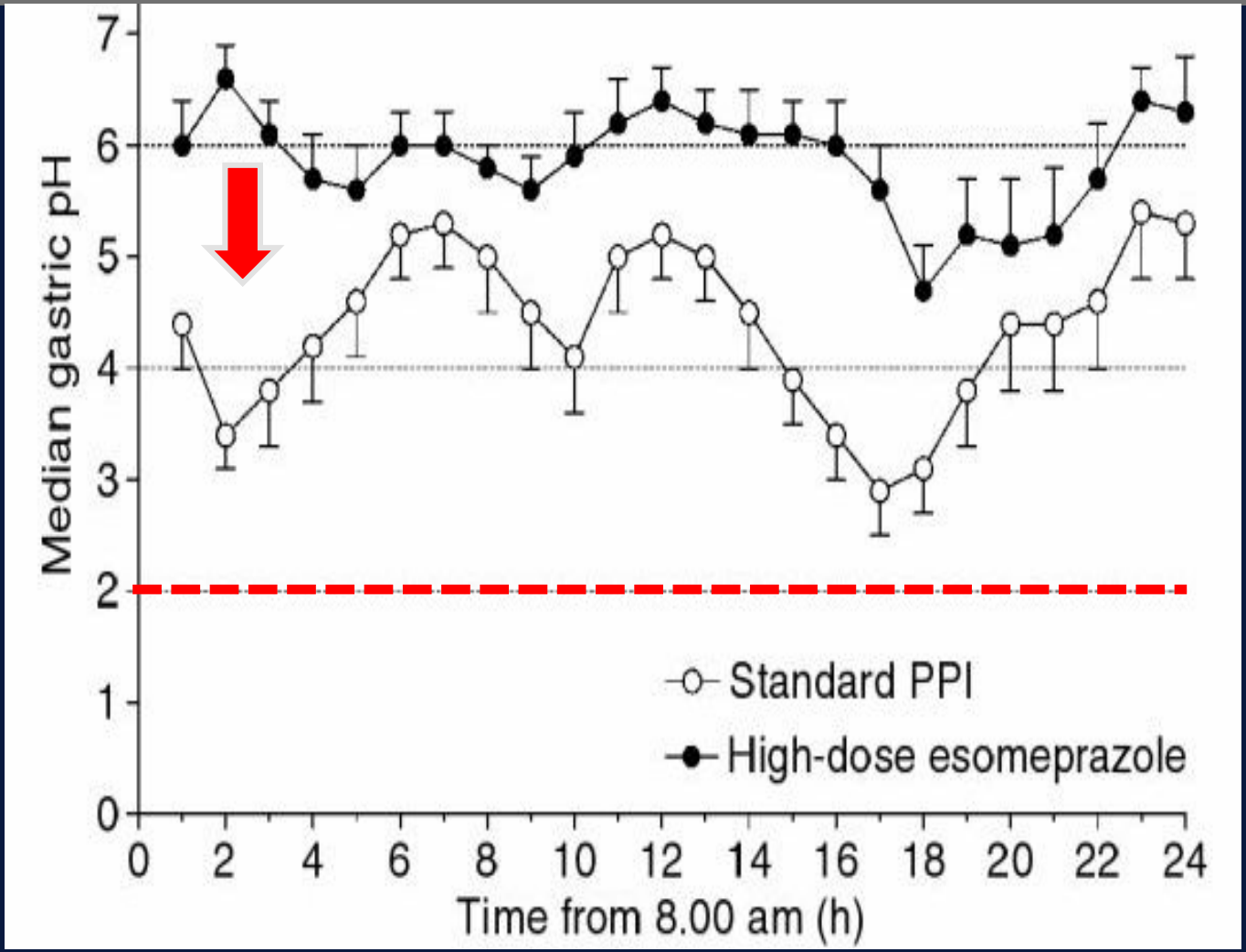
Proton Pump Inhibitors (PPI)

Parameter		Geometric Mean		%Geometric Mean Ratio (90% CI)
		LDV/SOF	+OME	LDV/SOF+OME Simultaneous/ LDV/SOF
LDV	C_{max}	178	158	89.1 (60.9, 130)
	AUC	6090	5840	96.0 (66.5, 139)
SOF	C_{max}	974	1090	112 (87.9, 142)
	AUC	1310	1310	100 (80.2, 125)
GS-331007	C_{max}	831	951	114 (101, 129)
	AUC	12100	12500	103 (95.5, 112)

- A PPI at a dose comparable to OME 20 mg may be administered simultaneously with LDV/SOF. PPIs should not be taken before LDV/SOF.

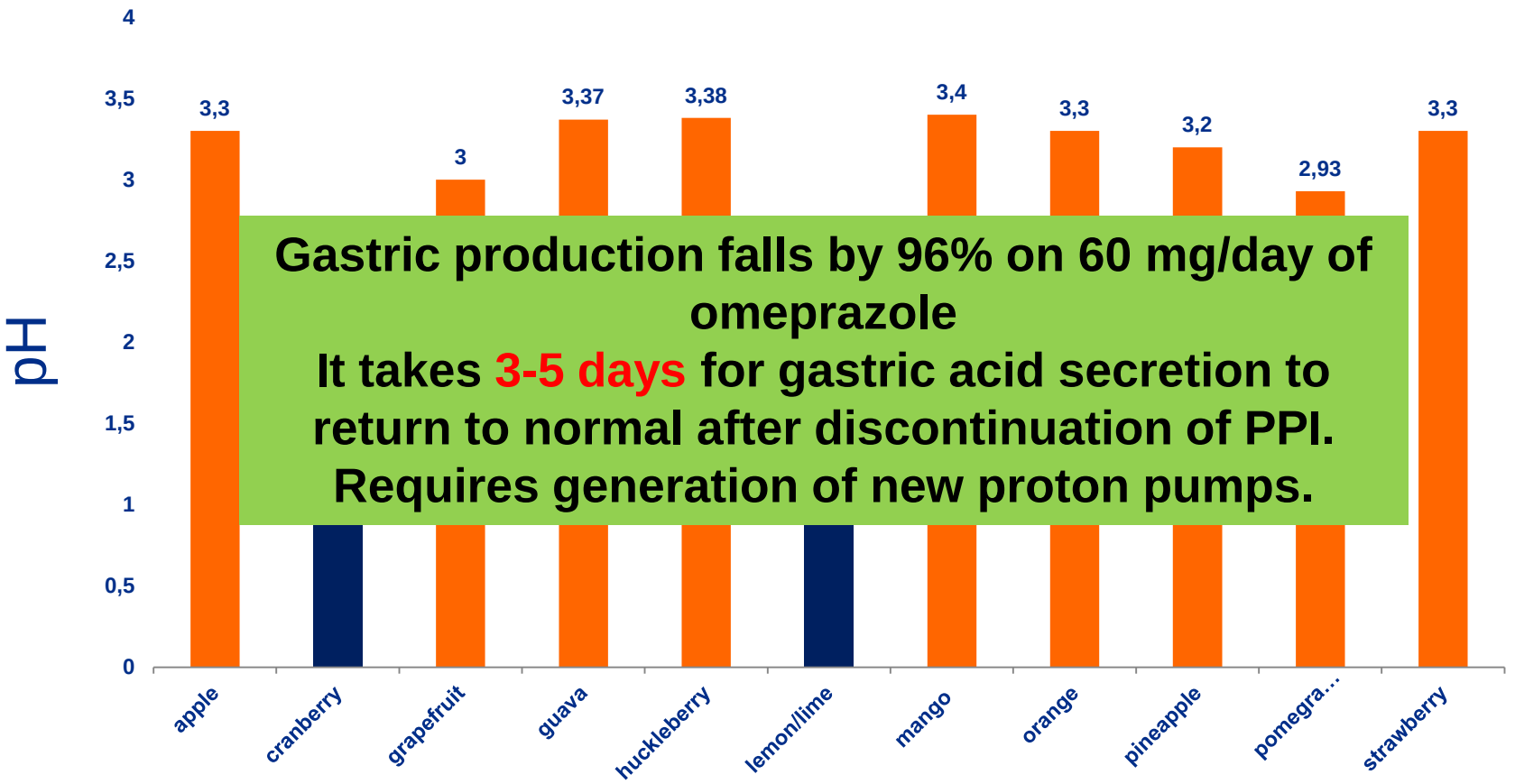
AUC_{inf} (ng*hr/ml)=area under the plasma concentration versus time curve extrapolated to infinite time; CI=confidence interval; C_{max}(ng/ml)=maximum observed plasma concentration of drug; OME: omeprazole 20 mg

Effect of Proton Pump Inhibition and Juices on Gastric pH



Abu-Sneineh A, et al. *Aliment Pharmacol Ther.* 2010;32(8):1023-1030.

Effect of Proton Pump Inhibition (PPI) and Juices on Gastric pH



US Food and Drug Administration. Omeprazole Magnesium Tablets October 20, 2000. Document #NDA No. 21-229. http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3650b1a_11.pdf.

Conclusions:
Acid Suppression

- Stop PPIs and transfer to H2 receptor agonists when possible
  - PPIs often started at LTx for reasons that do not persist (eg, MMF)
- If the patient must use a PPI, 20 mg/day equivalent of omeprazole, give with cranberry juice at same time as PPI