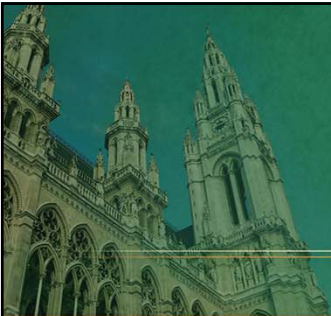




Advances in Chronic Hepatitis C Management and Treatment

REPORTING ON EASL 2015

Comprehensive Expert Review and Discussion of Key Presentations

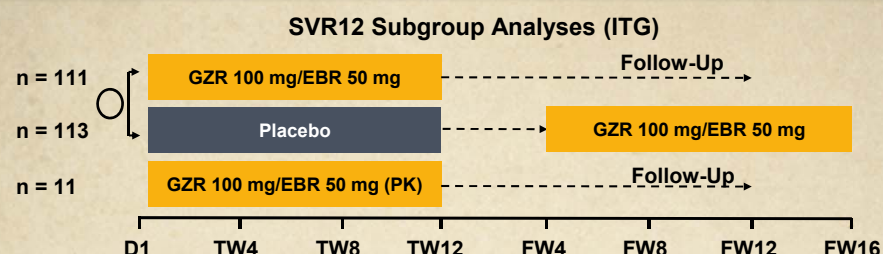
C-SURFER: GRAZOPREVRIR PLUS ELBASVIR IN TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE

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M.-C. Londoño, T. Hassanein, P. Zamor, E. Zuckerman, Y. Zhao, S. Wan,
B. Jackson, M. Robertson, J. Wahl, E. Barr, W. Greaves

Abstract LP02

C-SURFER: Study Design

SVR12 Subgroup Analyses (ITG)



The diagram illustrates the study design for SVR12 Subgroup Analyses (ITG). It shows three treatment arms over time (D1, TW4, TW8, TW12, FW4, FW8, FW12, FW16). The first arm (n=111) receives GZR 100 mg/EBR 50 mg from D1 to TW12, followed by follow-up. The second arm (n=113) receives Placebo from D1 to TW12, followed by GZR 100 mg/EBR 50 mg from FW4 to FW16. The third arm (n=11) receives GZR 100 mg/EBR 50 mg (PK) from D1 to TW12, followed by follow-up.

- 🌿 Randomized, parallel-group, multisite, placebo-controlled trial
- 🌿 Stratification by diabetes (yes/no) and hemodialysis status: hemodialysis or nonhemodialysis
- 🌿 224 patients randomized to immediate treatment (ITG) with GZR/EBR or deferred treatment (DTG) where patients received placebo for 12 weeks then open-label GZR/EBR starting at follow-up week (FW) 4
- 🌿 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic (PK) sampling

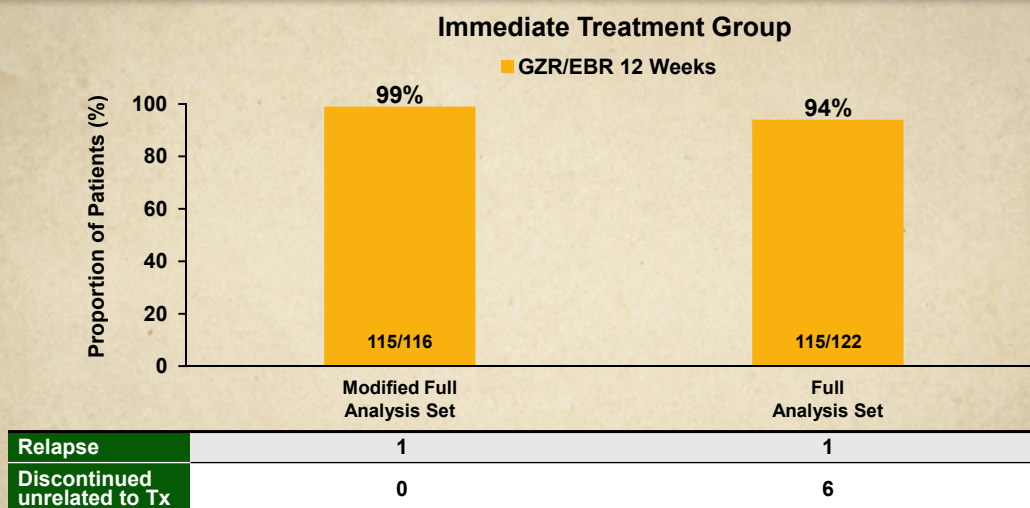
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Demographics

	GZR + EBR (ITG + PK) 12 Weeks (n =122)	Placebo (DTG) 12 Weeks (n =113)
Sex, n (%)		
Male	92 (75)	80 (71)
Female	30 (25)	33 (29)
Race, n (%)		
White	61 (50)	48 (43)
African American	55 (45)	53 (47)
Asian	5 (4)	9 (8)
Other	1 (<1)	3 (3)
HCV genotype, n (%)		
G1a	63 (52)	59 (52)
G1b	58 (48)	53 (47)
G1 other	1 (<1)	1 (<1)
Treatment history, n (%)		
Naïve	101 (83)	88 (78)
experienced	21 (17)	25 (22)
Cirrhosis, n (%)	7 (6)	7 (6)
Diabetes, n (%)	44 (36)	36 (32)
Dialysis, n (%)	92 (75)	87 (77)
CKD stage, n (%)		
4	22 (18)	22 (19)

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C-SURFER: SVR12 Results



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RAVs at Baseline and at Virologic Failure^a (ITG)

1 patient had virologic failure (relapse) at follow-up week (FW) 12

Failure Type	Genotype	Follow-up Day of Failure	RAVs ^a at Baseline		RAVs ^a at Failure	
			NS3	NS5A	NS3	NS5a
Relapse	G1b	84	WT	L31M	V170I	L31M, Y93H

^a Population sequencing
ITG = immediate treatment group; RAV = resistance associated variant; WT = wild type

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Laboratory Safety Summary

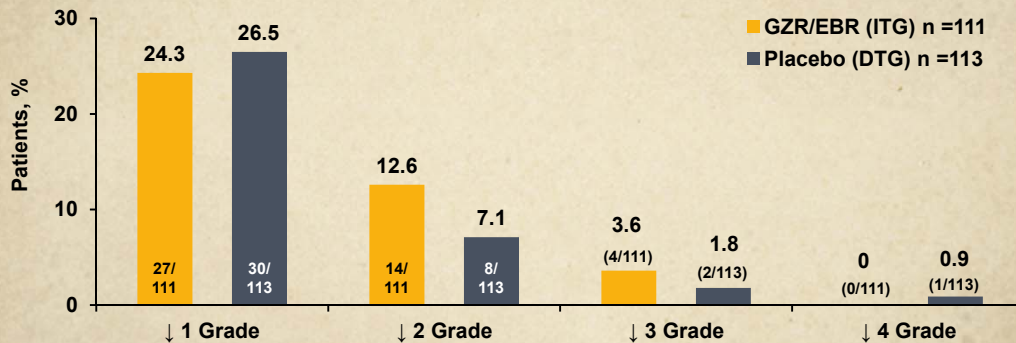
	GZR/EBR (ITG) 12 Weeks (n =111)	Placebo (DTG) 12 Weeks (n =113)	Difference in % Estimate (95% CI)
ALT, n (%)			
1.1-2.5 x baseline	2 (1.8)	36 (31.9)	-30.1 (-39.4, -21.5)
>2.5-5 x baseline	1 (0.9)	6 (5.3)	-4.4 (-10.3, 0.2)
>5 x baseline	0 (0)	1 (0.9)	-1.1 (-6.3, 3.2)
AST, n (%)			
1.1-2.5 x baseline	4 (3.6)	38 (33.6)	-30.0 (-39.6, -21.0)
>2.5 x baseline	0 (0)	4 (3.5)	-4.6 (-11.3, -0.2)
Total bilirubin, ^a n (%)			
>2.5-5.0 x baseline	1 (0.9)	3 (2.7)	-1.8 (-6.7, 2.5)
>5.0 x baseline	0 (0)	0 (0)	0.0 (-3.3, 3.4)
Alkaline phosphatase, n (%)			
1.1-2.5 x baseline	42 (37.8)	36 (31.9)	6.0 (-6.6, 18.3)
>2.5 x baseline	0 (0)	0 (0)	0.0 (-3.3, 3.4)

^a Bilirubin level elevations were isolated and not associated with increased alanine transaminase (ALT)/AST.

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Hemoglobin: On-Treatment Change from Baseline

- Patients with grade 3/4 change in hemoglobin (GZR/EBR, n=4; placebo, n=2)
 - All 4 patients receiving GZR/EBR and 1 of 2 patients receiving placebo had a history of anemia (requiring intermittent EPO) or chronic ASA use
- ESA was used by 24% of patients receiving GZR/EBR and 30% of patients receiving placebo



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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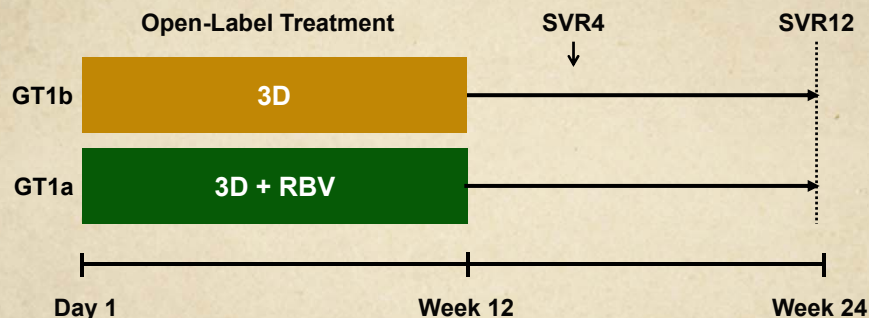
SAFETY OF OMBITASVIR/PARITAPREVIR/RITONAVIR PLUS DASABUVIR FOR TREATING HCV GT1 INFECTION IN PATIENTS WITH SEVERE RENAL IMPAIRMENT OR END-STAGE RENAL DISEASE: THE RUBY-I STUDY

Paul J Pockros, K Rajender Reddy, Parvez S Mantry, Eric Cohen, Michael Bennett, Mark S Sulkowski, David Bernstein, Thomas Podsadecki, Daniel Cohen, Nancy S Shulman, Deli Wang, Amit Khatri, Manal Abunimeh, Eric Lawitz

Abstract LO1

RUBY-I: Safety of 3D + DSV for Treating GT1 in Severe Renal Impairment or Endstage Renal Disease

- Chronic Kidney Disease with Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m²
- Multicenter, Open-label, Phase 3b Study, 9 sites, all in the United States



- 3D:** Co-formulated OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg BID)
- For GT1a:** RBV 200 mg QD
- For GT1b:** No RBV

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Baseline Demographics, Clinical Characteristics

	3D±RBV N=20
Male; n (%)	17 (85)
Black; n (%)	14 (70)
Age, years; median (range)	60 (49-69)
Hispanic or Latino ethnicity; n(%)	3 (15)
Degree of fibrosis; n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV viral load, log ₁₀ (IU/mL); median (range)	6.6 (5.5-7.6)
GT1a; n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage; n (%)	
4 (eGFR 15-30 mL/min/1.73m ²)	7 (35)
5 (eGFR <15 mL/min/1.73m ² or requiring dialysis)	13 (65)
On dialysis; n (%)	13 (65)
eGFR, mL/min/1.73m ² ; median (range)	10.9 (5.4-29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2-10.8)

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Efficacy

- All viral loads suppressed rapidly on treatment
- There are no virologic failures to date
- All 10 patients who reached PTW4 to date achieved SVR4

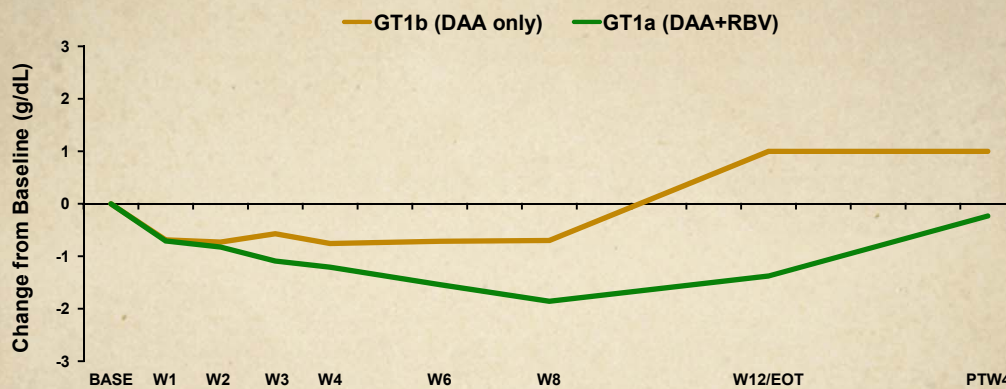
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
GT*	1a	1a	1a	1a	1b	1a	1a	1a	1a	1a	1b	1a	1a	1a	1b	1b	1b	1b	1b	1a
Renal Stage	4	4	5	5	5	5	5	4	5	5	5	5	4	4	5	4	5	5	5	5
BASE (x1000)	746	25300	17100	3520	2980	429	1730	43300	12600	6670	9820	292	6980	2570	3680	383	1230	6500	1850	4210
W1																				
W2																				
W4																				
W8																				
W12EOT																				
PTW4																				
PTW12																				
PTW24																				

HCV RNA: ■ ≥ 25 IU/mL ■ < 25 IU/mL ■ Undetectable

*3D: GT1b; 3D+RBV: GT1a

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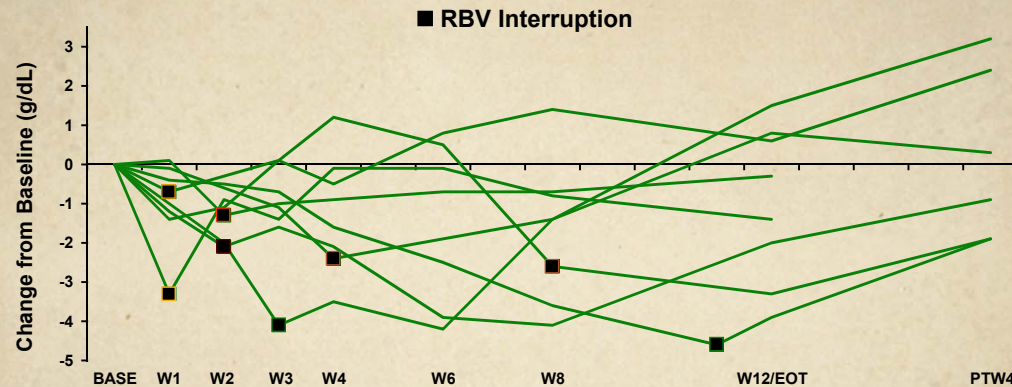
Hematologic Impact of RBV (Mean Change in Hgb [g/dL])



GT1b: N =	7	7	7	7	7	7	5	2	2
GT1a: N =	13	13	13	13	13	12	12	12	9

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Hematologic Impact of RBV (Change in Hgb [g/dL] Over Time)



- 8/13 GT1a patients interrupted RBV while on treatment
- 1 patient had a hemoglobin value <8 g/dL
- No patients had blood transfusions
- Of the 8 patients who interrupted RBV, 4 started EPO (week 1-7)

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Adverse Events

	GT1b 3D N=7	GT1a 3D+RBV N=13
Event ^a (experienced by 2 or more patients)	n	
Anemia	0	8
Fatigue	2	4
Diarrhea	1	4
Nausea	0	5
Dizziness	1	2
Headache	0	3
Decreased appetite	0	2
Irritability	0	2
Edema peripheral	1	1
Weight decreased	0	2

^aAdverse event as reported by investigator.

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Pharmacokinetics

- 🔗 Preliminary pharmacokinetic data are available for 17 patients
- 🔗 The preliminary mean C_{trough} values of DAAs in HCV-infected patients with stage 4 and 5 CKD are comparable to those in patients without renal impairment (historical data)

	Mean C_{trough} (RUBY-I) (ng/mL)	Mean C_{trough} (Range across 5 Phase 3 studies) (ng/mL)
Paritaprevir	36	16 to 29
Ritonavir	50	40 to 53
Ombitasvir	36	24 to 30
Dasabuvir	253	177 to 270
Ribavirin	1088	2180 to 2330

Mean C_{trough} computed using binned concentration time profile

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