ADVANCES IN CHRONIC HEPATITIS C:
MANAGEMENT AND TREATMENT
REPORTING ON EASL 2016
COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS
AN INDEPENDENT CME ACTIVITY JOINTLY PROVIDED BY POSTGRADUATE INSTITUTE FOR MEDICINE AND VIRALED, INC.
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C-SWIFT RETREATMENT FINAL RESULTS: HIGHLY SUCCESSFUL RETREATMENT OF GT1-INFECTED PATIENTS WITH 12 WEEKS OF ELBASVIR/GRAZOPREVIR PLUS SOFOSBUVIR AND RIBAVIRIN AFTER FAILURE OF SHORT-DURATION ALL-ORAL THERAPY

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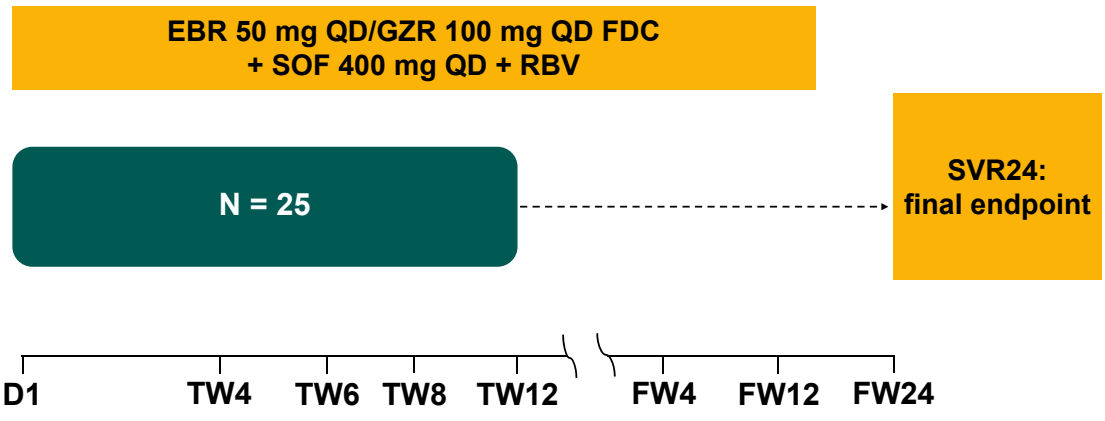
Abstract SAT-148

Study Design



SVR24 = Final endpoint (HCV RNA < 15 IU/mL),

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Patient Demographics

	GENOTYPE 1 12 Weeks n = 25
Male, n (%)	22 (88)
Age, mean yr (range)	54 (23-66)
Race, White, n (%) Ethnicity: Hispanic or Latino, n (%)	25 (100) 11 (44)
IL28B (*IFNL3*) CC, n (%)	5 (20)
HCV Genotype or Subtype, n (%) G1a G1b	 22 (88) 3 (12)
Cirrhosis, n (%)	5 (20)
Mean baseline viral load (log_{10} IU/ML)	6.19
Patients with Baseline RAV, n (%) NS5A NS3 NS5B NS5A + NS3	 19 (76) 13 (52) 0 (0) 11 (44)

RAV = resistance associated variant

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Prevalence of NS5A RAVs at Baseline*

NGS sensitivity	POSITION					
	WT	28	30	31	58	93
1%	6 (24%)	8 (32%)	9 (36%)	7 (28%)	6 (24%)	4 (16%)
10%	11 (44%)	6 (24%)	7 (28%)	2 (8%)	4 (16%)	2 (8%)
15%	12 (48%)	5 (20%)	7 (28%)	2 (8%)	4 (16%)	2 (8%)

*According to NGS assay sensitivity and amino acid position
RAV = resistance associated variant

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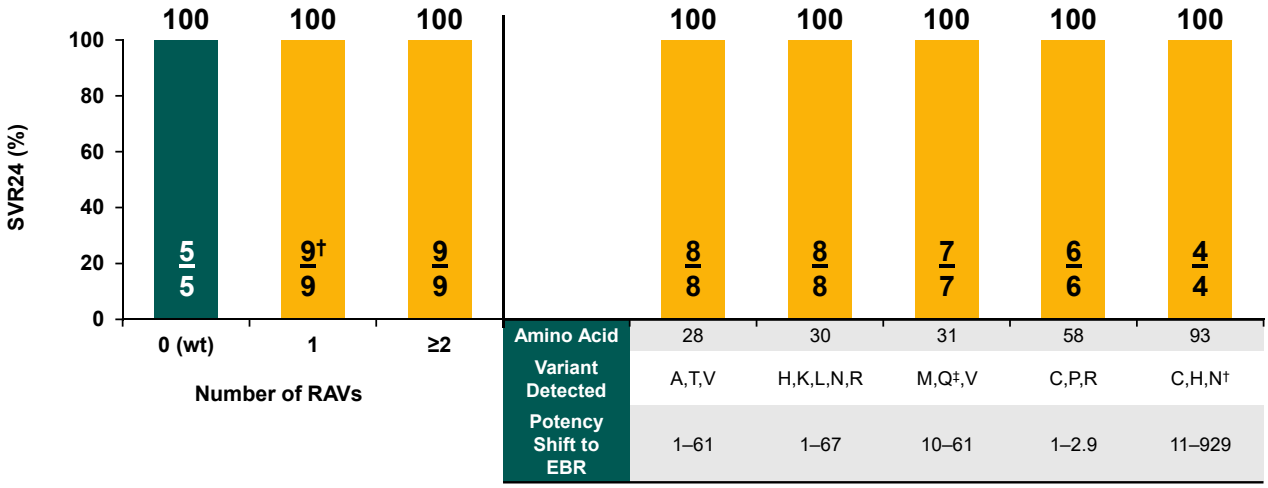
SVR24 by Baseline NS5A RAVs (mFAS)



†Includes 1 patient who had population sequencing and had 1 RAV detected (Y93N)
‡No data on potency shift of NS5A:Q31 to EBR
RAV = resistance-associated variant (next-generation sequencing, sensitivity threshold 1%)

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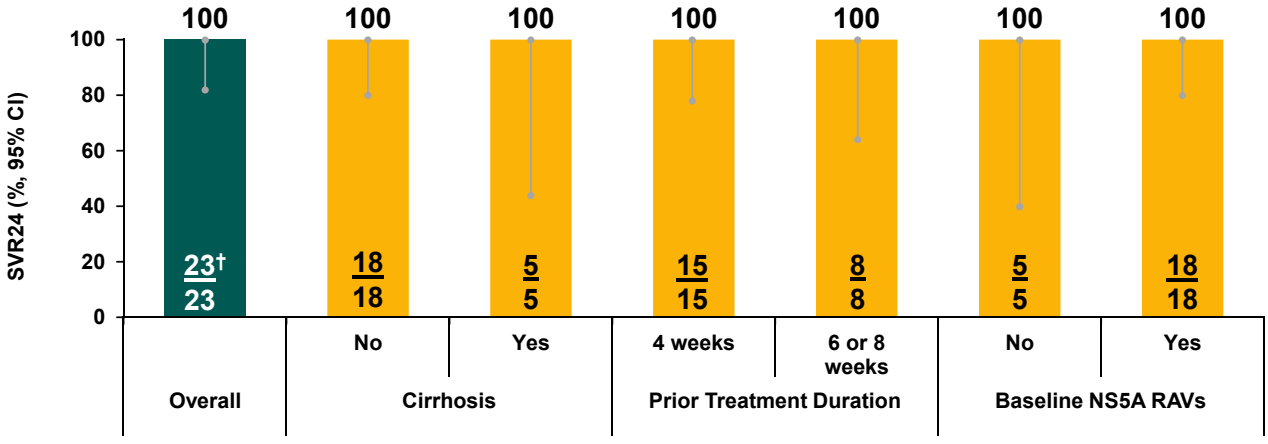
SVR24: Overall and by Subgroup (mFAS)



†Excludes two patients lost to follow-up at day 3 and treatment week 4
RAV = resistance-associated variant (next-generation sequencing, sensitivity threshold 1%)

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Ribavirin Safety and Tolerability

Hemoglobin

- Lowest hemoglobin during treatment: 9.7 gm/dL

Dose Modification

- 1 patient discontinued RBV at TW4 due to pruritus
- 1 patient decreased RBV due to anemia at TW6

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Conclusions

Efficacy

- A 12 week regimen of EBR/GZR + SOF + RBV successfully treated GT1-infected patients who failed short duration EBR/GZR + SOF
  - 100% SVR24 was achieved regardless of cirrhosis, baseline RAVs (including patients with linked RAVs or 2 classes of RAVs), or subgenotype
  - High efficacy was achieved regardless of NGS sensitivity threshold

Safety

- A 12 week regiment of EBR/GZR + SOF + RBV was generally safe and well tolerated
- Two patients required RBV dose adjustment and both achieved SVR24

RAV = resistance associated variant

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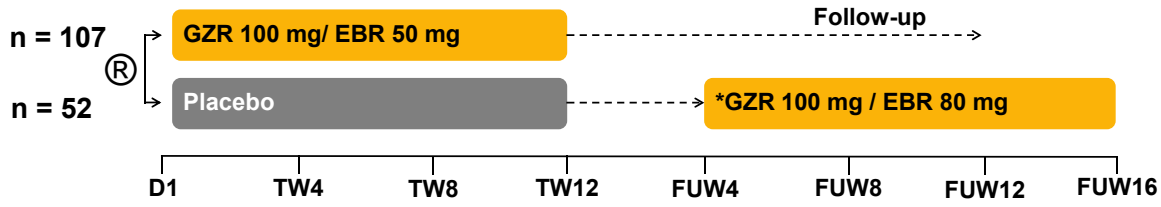
C-EDGE IBLD: EFFICACY AND SAFETY OF ELBASVIR/GRAZOPREVIR (EBR/GZR) IN SUBJECTS WITH CHRONIC HEPATITIS C VIRUS INFECTION AND INHERITED BLOOD DISORDERS

Christophe Hezode, Massimo Colombo, Ulrich Spengler, Ziv Ben-Ari, Simone Strasser, William M. Lee, Leslie Morgan, Jingjun Qiu, Peggy Hwang, Michael Robertson, Bach-Yen Nguyen, Eliav Barr, Janice Wahl, Barbara Haber, Rohit Talwani, Vito Di Marco

Abstract SAT-128

Study Design



- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by cirrhosis (yes/no) and disease status (sickle cell anemia versus thalassemia versus hemophilia/von Willebrand disease)
- 159 patients randomized to immediate treatment with EBR/GZR or deferred treatment where patients received placebo for 12 weeks and then open-label EBR/GZR starting at FUW4

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Demographics

	GZR + EBR (Immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Gender, n (%)		
Male	80 (74.8)	39 (75.0)
Female	27 (25.2)	13 (25.0)
Race, n (%)		
White	81 (75.7)	40 (76.9)
African-American	19 (17.8)	9 (17.3)
Asian	6 (5.6)	3 (5.8)
Other	1 (0.9)	0 (0)
HCV genotype, n (%)		
G1a	47 (43.9)	18 (34.6)
G1b	46 (43.0)	27 (51.9)
G1 other	2 (1.9)	0 (0)
G4	12 (11.2)	6 (11.5)
G6	0 (0)	1 (1.9)
Prior treatment history, n (%)		
Naïve	53 (49.5)	27 (51.9)
Experienced	54 (50.5)	25 (48.1)
Cirrhosis, n (%)	26 (24.3)	12 (23.1)
HIV coinfected, n (%)	6 (5.6)	4 (7.7)
IL28B CC, n (%)	27 (25.2)	9 (17.3)
Blood disorder, n (%)		
Sickle Cell Anemia	19 (17.8)	10 (19.2)
β Thalassemia	41 (38.3)	20 (38.5)
von Willebrand / Hemophilia A/B	47 (43.9)	22 (42.3)

DTG = deferred treatment group; ITG = immediate treatment group

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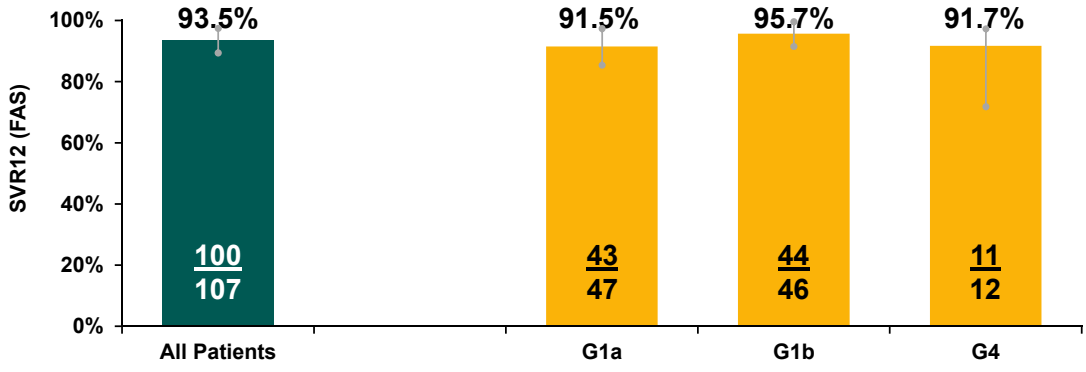
SVR12: Primary Efficacy Analysis Immediate Treatment Group, Full Analysis Set



	All Patients	G1a	G1b	G4
Breakthrough	0	0	0	0
Relapse	6	4	1	1
LTFU/Early DC	1	0	1	0
SVR12 (mFAS)	100/106 (94.3%)	43/47 (91.5%)	44/45 (97.8%)	11/12 (91.7%)

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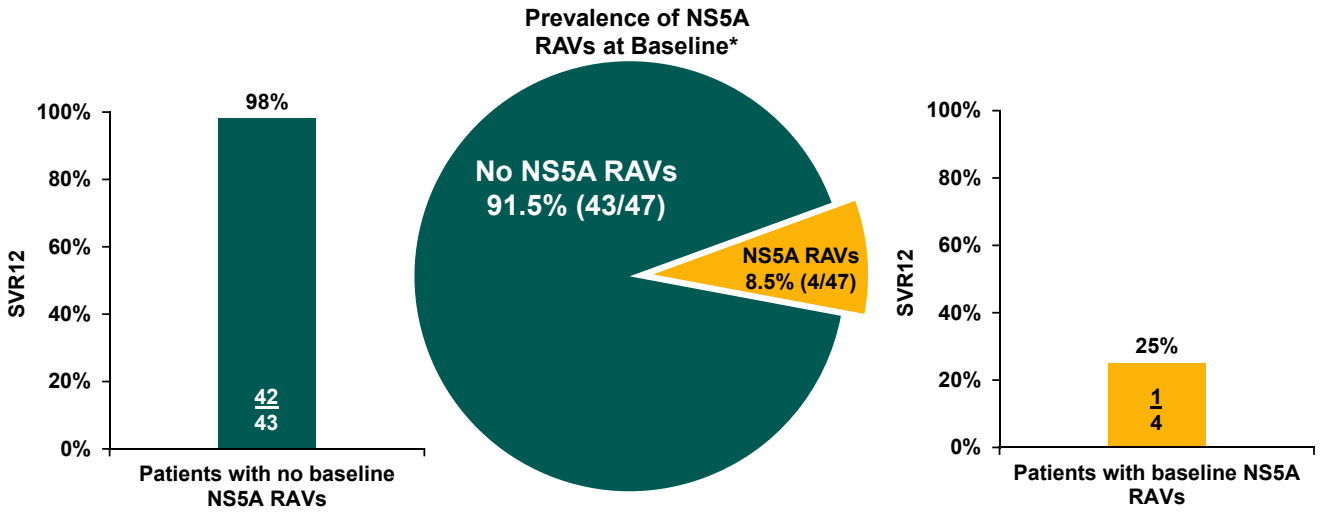
NS5A Resistance Associated Variants in Patients with HCV G1A Infection



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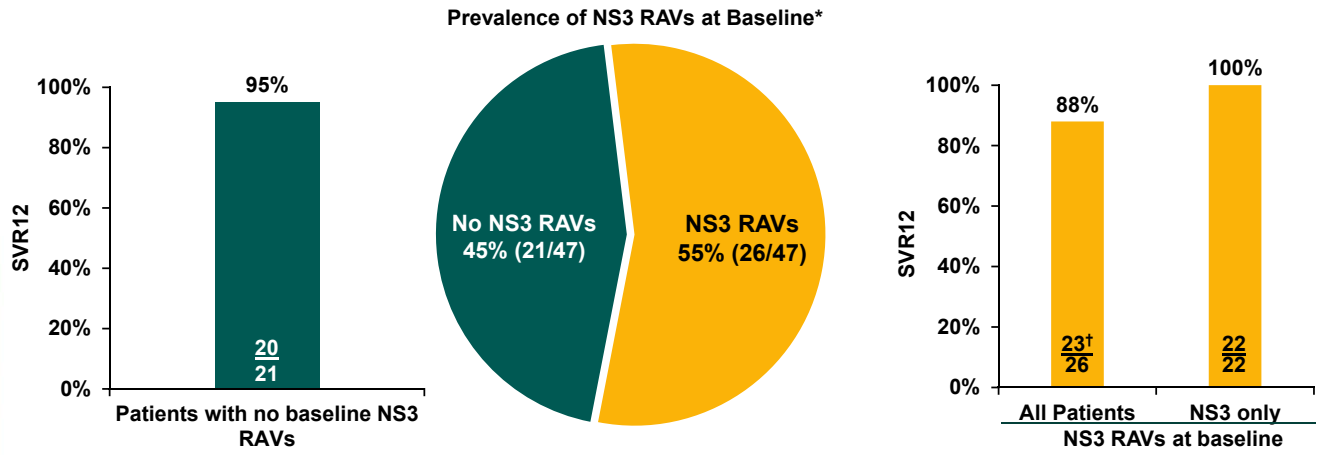
NS3 Resistance Associated Variants in Patients with HCV GT1A Infection



A pooled analysis of the phase 2/3 EBR/GZR clinical program demonstrated that 146/147 (99%) of TM GT1a subjects with baseline NS3 RAVs without the baseline NS5A RAVs achieved a SVR12 while univariate logistic regression models of TE and GT1a subjects failed to show an association between baseline NS3 RAVs and lower treatment response rates[1]

[1]Zeuzem et al. Predictors of Response to Grazoprevir/Elbasvir Among HCV Genotype 1 (GT1)–Infected Patients: Integrated Analysis of Phase 2-3 Trials. Presented at the Annual Meeting of the American Association For Study of The Liver, Nov 13-17, San Francisco, CA, USA. [Abstract 700]; Hezode C, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. SAT-128.

Characteristics of Patients with Virologic Failure: All Relapses

- Relapse patients generally had baseline viral load >2M IU/mL and NS5A RAVs at baseline

Patient ID	Inherited blood disorder	Genotype	Cirrhosis	Baseline viral load (IU/mL)	First day on treatment of undetectable HCV RNA	VF	Follow-up day of relapse	NS3 RAVs		NS5A RAVs	
								At baseline	At failure	At baseline	At failure
43y, TN, Thai female	Beta-thalassemia	G1a	No	9.07×10^5	29	Relapse	56	S122S/G	I170V	Q30L/Q, Y93Y/H	Y93N
43y, TN, white male	Factor VIII deficiency	G1a	No	2.02×10^6	60	Relapse	28	none	A156T/A	none	Q30R, L31M
60y, TN, HIV+, white male	Factor VIII deficiency	G1a	No	4.29×10^6	57	Relapse	27	Q80K	Y56H, Q80K, D168A (FU8)	Y93C	L31M, Y93C
47y, TN, white male	Factor VIII deficiency	G1a	No	4.51×10^6	29	Relapse	56	Q80K	Q80K	M28V	M28A, Q30R
41y, TN, white male	Factor VIII deficiency	G1b	No	2.24×10^6	50	Relapse	86	T54S, V55I	T54S, V55I, R155L/R	R30Q, L31M	R30Q, L31M, Y93H
47y, TN, black female	Sickle cell anemia	G4	No	1.97×10^6	29	Relapse	57	D168E	D168E	L28M, L30H	L28M, L30H, H93C

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Adverse Events

	GZR + EBR (Immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Any adverse event, n (%)	77 (72.0)	33 (63.5)
Headache	23 (21.5)	6 (11.5)
Fatigue	18 (16.8)	4 (7.7)
Nausea	9 (8.4)	8 (15.4)
Asthenia	8 (7.5)	2 (3.8)
Abdominal pain	7 (6.5)	2 (3.8)
Arthralgia	7 (6.5)	3 (5.8)
Pyrexia	6 (5.6)	0 (0)
Nasopharyngitis	6 (5.6)	2 (3.8)
Drug related AE, n (%)	36 (33.6)	16 (30.8)
Serious AE[†], n (%)	3 (2.8)	6 (11.5)
Discontinued due to an AE, n (%)	0 (0)	1[‡] (1.9)
Death, n (%)	0 (0)	0 (0)

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Liver Enzymes

	GZR + EBR (Immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Alanine aminotransferase, n (%)		6 (11.5)
Grade 3: 5.1 – 10.0 x ULN	0 (0)	1 (1.9)
Grade 4: >10.0 x ULN	1 (0.9)	
Aspartate aminotransferase, n (%)		
Grade 3: 5.1 – 10.0 x ULN	1 (0.9)	2 (3.8)
Grade 4: >10.0 x ULN	0 (0)	1 (1.9)
ALT/AST >500IU/L, n (%)	0 (0)	1 (1.9)
ALT/AST >3 x baseline and >100 IU/L, n (%)	1 (0.9)	1 (1.9)
Bilirubin, n (%)		
Grade 3: 2.6 – 5.0 x ULN	12 (11.2)	9 (17.3)
Grade 4: >5 x ULN	8 (7.5)	3 (5.8)
>2.5-5 x baseline	2 (1.3)	0 (0)
>5x baseline	0 (0)	0 (0)
Alkaline phosphatase >3x ULN, n (%)	0 (0)	0 (0)

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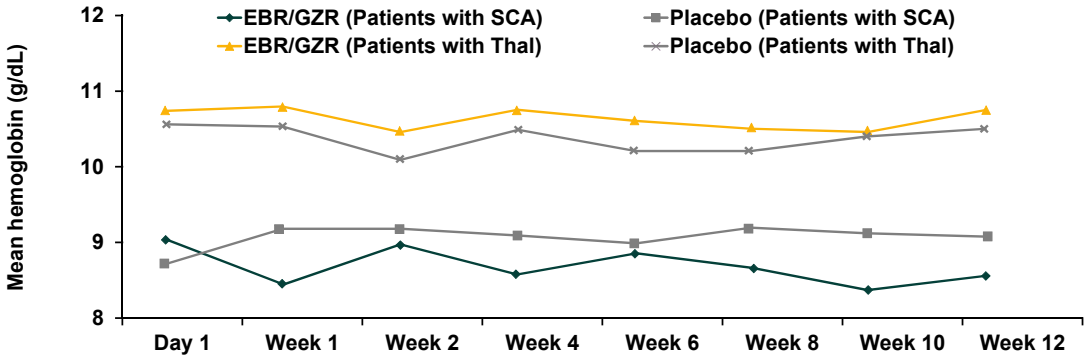
On-Treatment Hemoglobin Levels



		Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Sickle cell patients (n)	EBR/GZR	17	15	18	18	18	18	17	16
	Placebo	8	9	8	10	9	9	7	8
Thalassemia patients (n)	EBR/GZR	38	39	40	40	41	41	40	40
	Placebo	17	19	19	19	20	20	19	19

SCA = sickle cell anemia; Thal =thalassemia

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Conclusions

- A 12 week regimen of EBR/GZR was highly efficacious among patients with inherited blood disorders and HCV G1/4 infection
- High efficacy was maintained across many important patient subgroups including those with cirrhosis and HIV coinfection, and across all inherited blood disorders
  - A lower response was seen among GT1a patients with baseline NS5A RAVS
- EBR/GZR is generally well tolerated when administered to patients with inherited blood disorders and HCV infection
- EBR/GZR had no impact on measures of hematology and clotting, and no impact on the treatment of the underlying blood disorder

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