Prevalence and Impact of Baseline Resistance-Associated Variants on the Efficacy of Elbasvir/Grazoprevir in Hepatitis C Genotype 1-Infected Japanese Patients

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Introduction

- Elbasvir (EBR) is a potent hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir (GZR) is a potent NS3/4A inhibitor
- The Phase 3 portion of a Phase 2/3 study evaluated the efficacy and safety of the combination of EBR/GZR given once daily in genotype 1 (GT1)-infected, mostly GT1b-infected treatment-naïve or IFN-experienced Japanese chronic hepatitis C (CHC) patients with or without cirrhosis
- In the full analysis set (FAS) population for GT1b patients, coadministration of EBR/GZR for 12 weeks resulted in SVR24 of 96.4%
  - Only 1.8% (6/335) of GT1a patients were included, and all of them achieved SVR24
- EBR/GZR was largely safe and well tolerated

Objectives

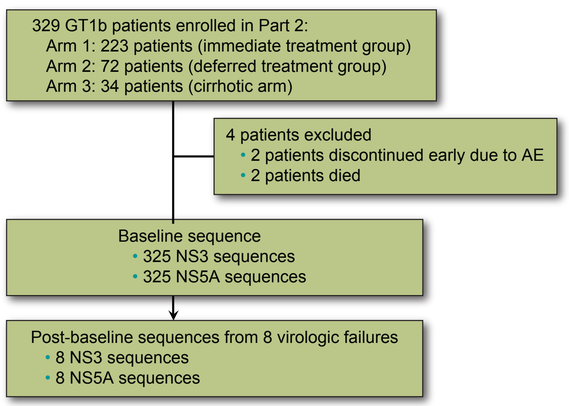
In Japanese GT1b-infected patients with CHC, with or without cirrhosis, in the Phase 3 portion of a Japanese Phase 2/3 study:

- To evaluate the prevalence and types of NS3 and NS5A variants at baseline
- To determine the impact of baseline variants on treatment response in subjects treated with EBR/GZR
- To identify and characterize the post-treatment resistance-associated variants (RAVs) in virologic failures (VFs)

Methods

- Resistance analyses were conducted on the resistance analysis population (RAP), which included all subjects from the FAS population who either achieved SVR24 or met the criteria for VF (**Figure 1**)
  - Four patients excluded from the RAP: 2 patients discontinued early due to adverse events (AEs) and 2 patients died before follow-up week 12
- Plasma samples from all patients at day 1, pre-dosing, and at follow-up visits in patients with confirmed VF were evaluated by population sequencing (Pop seq) of NS3 and NS5A genes
- These samples were further analyzed by whole-genome next-generation sequencing (NGS; also called deep sequencing) in duplicate

Figure 1. Resistance analysis population (RAP)



Results

Table 1. Demographics

Factors		Noncirrhotic: EBR + GZR (Immediate)	Noncirrhotic: Placebo (Deferred)	Cirrhotic: EBR + GZR
Total		223†	72‡	34
Gender	Male, n : Female, n	84 : 139	20 : 52	17 : 17
Age	Median years (range)	63 (21-80)	63 (34-80)	65.5 (43-79)
	<65, n (%)	119 (53%)	39 (54%)	15 (44%)
	≥65, n (%)	104 (47%)	33 (46%)	19 (56%)
HCV subtype, n (%)	GT1b	223 (100%)	72 (100%)	34 (100%)
Prior treatment, n (%)	Naïve	147 (66%)	48 (67%)	20 (59%)
	Intolerant to prior P/R	11 (5%)	3 (4%)	3 (9%)
	Relapse to prior P/R	39 (17%)	13 (18%)	6 (18%)
	Nonresponse to prior P/R	26 (12%)	8 (11%)	5 (15%)
IL28B, n (%) (rs12979860)	Major (CC)	130 (58%)	43 (60%)	22 (65%)
	Minor (TC)	83 (37%)	28 (39%)	12 (35%)
	Minor (TT)	10 (5%)	1 (1%)	0 (0%)
Baseline HCV RNA, median log IU/mL (range)		6.3 (4.7-7.2)	6.3 (4.8-7.3)	6.5 (5.1-7.1)

†Three patients excluded from the RAP: 2 patients discontinued early due to AE and 1 patient died before follow-up week 12.
‡One patient excluded from the RAP: died before follow-up week 12.

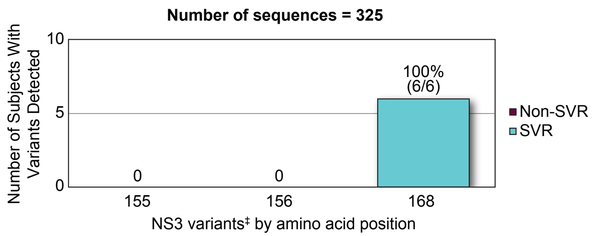
Pop Seq Results

- The specific loci analyzed include NS3 amino acid positions 155, 156, and 168, specifically R155X*, A156S/T/V/F/G, and D168X*

*X following a sequence position signifies that any variant (ie, different from the reference sequence) at that position is reported/

- The prevalence of baseline NS3 variants was 1.8% (6/325)
- SVR24 rates in GT1b subjects without or with baseline NS3 variants were 97.5% (311/319) or 100% (6/6), respectively (**Table 2**)
- There was no impact of baseline NS3 variants on SVR24 rates

Figure 2/Table 2. Prevalence and impact of baseline NS3 variants on efficacy

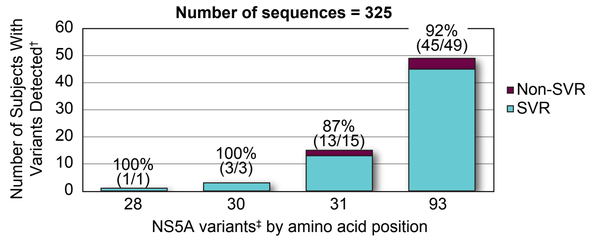


Population	SVR24 (%): Overall Efficacy in Subjects With Sequence in RAP	NS3 Variants‡ Not Detected	NS3 Variants‡ Detected
Overall RAP	317/325 (97.5%)	311/319 (97.5%)	6/6 (100%)

SVR24 (%) = number of subjects achieving SVR24/total number of subjects (RAP).
‡NS3 variants: R155X, A156S/T/V/F/G, and D168X (X following a sequence position signifies that any at that position is reported) detected by population sequencing (sensitivity threshold: 25%).

- The specific loci analyzed include NS5A amino acid positions 28, 30, 31, and 93, specifically L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, and Y93C/H/N/S
- The prevalence of baseline NS5A variants was 19.7% (64/325)
- The most common baseline NS5A polymorphisms in the overall RAP were variants at position 93 (**Figure 3**)
- SVR24 rates in GT1b subjects without or with baseline NS5A variants were 98.9% (258/261) or 92.2% (59/64), respectively (**Table 3**)

Figure 3/Table 3. Prevalence and impact of baseline NS5A variants on efficacy



Population	SVR24 (%): Overall Efficacy in Subjects With Sequence in RAP	NS5A Variants‡ Not Detected	NS5A Variants‡ Detected
Overall RAP	317/325 (97.5%)	258/261 (98.9%)	59/64 (92.2%)

SVR24 (%) = number of subjects achieving SVR24/total number of subjects (RAP).
†Patients who have 2 or more baseline NS5A RAVs were counted in any applicable amino acid position.
‡NS5A variants: L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, and Y93C/H/N/S detected by population sequencing (sensitivity threshold: 25%).

- Y93H was detected in all 8 failures at failure point by Pop seq (**Table 4**)
- Y93H was detected in 4 patients at baseline, and the remaining 4 failures had Y93H as a treatment-emergent RAV
- All L31M and all Y93H detected at failure point persisted through FU24 (**Table 4**)

Table 4. Virologic failures and detected RAVs by Pop Seq

Subject #	Baseline NS3	Baseline NS5A	At Virologic Failure NS3	At Virologic Failure NS5A	Follow-up Week 4 NS3	Follow-up Week 4 NS5A	Follow-up Week 12 NS3	Follow-up Week 12 NS5A	Follow-up Week 24 NS3	Follow-up Week 24 NS5A
#1	WT	WT	WT	Y93H	WT	Y93H	WT	Y93H	WT	Y93H
#2	WT	L31M	WT	(L31M), Y93H	WT	(L31M), Y93H	WT	(L31M), Y93H	WT	(L31M), Y93H
#3	WT	WT	NA	NA	NA	NA	WT	Y93H	WT	Y93H
#4	WT	Y93H	WT	(Y93H)	TND†	TND†	WT	(Y93H)	WT	(Y93H)
#5	WT	Y93H	WT	L31M, (Y93H)	TND†	TND†	WT	L31M, (Y93H)	WT	L31M, (Y93H)
#6	WT	WT	WT	L31M, Y93H	TND†	TND†	WT	L31M, Y93H	WT	L31M, Y93H
#7	WT	L31M, Y93H	WT	(L31M), (Y93H)	TND†	TND†	WT	(L31M), (Y93H)	WT	(L31M), (Y93H)
#8	WT	Y93H	WT	L31V, (Y93H)	TND†	TND†	WT	L31V, (Y93H)	WT	L31V, (Y93H)

†These patients relapsed after follow-up week 4.
- Baseline variants persisting through virologic failure are indicated in parentheses.
- WT = wild type; NA = not applicable; TND = target not detected.
- Selected variants (NS3): R155X, A156S/T/V/F/G, D168X (X following a sequence position signifies that any at that position is reported).
- Selected variants (NS5A): L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, Y93C/H/N/S.

Next-Generation Sequencing Results

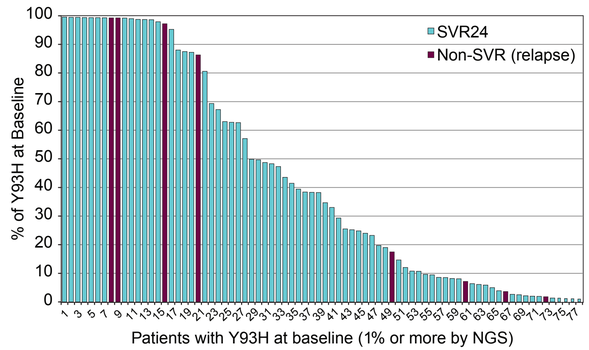
- All 325 baseline sequences data were available
- The SVR24 rates were 87% (27/31), 100% (25/25), and 82% (18/22) when Y93H was present at a detection rate of 1% to 20%, >20 to 80%, and >80 to 100%, respectively (**Table 5**)
  - The SVR24 rates by detection rate of baseline L31M showed the same tendency (**Table 5**)
- The detection rates of baseline Y93H in individual patients had no impact to SVR24 rates (**Figure 4**)

Table 5. Impact of baseline Y93H and L31M on efficacy by NGS detection rates

Baseline RAVs	<1%	1% to 20%	>20% to 40%	>40% to 60%	>60% to 80%	>80% to 100%
Y93H	100% (247/247)	87% (27/31)	100% (12/12)	100% (8/8)	100% (5/5)	82% (18/22)
L31M	98% (295/300)	90% (9/10)	100% (2/2)	100% (1/1)	100% (1/1)	82% (9/11)

Includes patients who have 2 or more baseline NS5A RAVs.

Figure 4. Individual patients with Y93H at baseline (1% or more by NGS)



Includes patients who have 2 or more baseline NS5A RAVs

Conclusion

NS3 RAVs

- The prevalence of NS3 baseline variants was low, and there was no impact on treatment response
- No NS3 post-treatment RAVs were observed

NS5A RAVs

- L31M and Y93H were the most prevalent NS5A baseline RAVs
- Regardless of presence of baseline NS5A variants, the SVR24 in GT1b patients still exceeds 92%
- The increased detection of baseline Y93H in individual patients by NGS revealed no impact on SVR24 rates
- The most prevalent post-treatment NS5A RAVs was Y93H

Disclosures

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- Yoshiyasu Karino - Speaking and Teaching: BMS K.K.
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