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Efficacy and Safety of Elbasvir/Grazoprevir in Hepatitis C Virus GT1- and GT4-Infected People Aged 65 Years or Older

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Abstract

Background: In elderly individuals aged ≥65 years with hepatitis C virus (HCV) infection, efficacious and safe HCV therapy is complicated by frequent comorbidities and concomitant medications. The aim of this analysis was to evaluate the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) in people aged ≥65 years. **Methods:** This is an integrated retrospective analysis of EBR/GZR administered for 12 weeks in participants with HCV genotype 1 or 4 infection enrolled in 12 Phase 2/3 clinical trials. The primary end point was sustained virologic response 12 weeks after completing therapy (SVR12; HCV RNA below the lower limit of quantification). **Results:** Most participants aged ≥65 years were receiving ≥1 concomitant medication (322/339; 95.0%) and had ≥1 comorbidity (334/339; 99%). SVR12 rates were 95.3% (323/339) in participants aged ≥65 years and 95.4% (2,041/2,139) in those aged <65 years. Rates of adverse events, drug-related adverse events, serious adverse events, and discontinuations were similar in participants aged ≥65 years and those aged <65 years. In participants aged ≥65 years, median estimated glomerular filtration rate was similar at baseline and at the end of treatment. **Conclusion:** The efficacy and safety of EBR/GZR were similar in participants with HCV infection aged ≥65 years and those aged <65 years.

Keywords

therapy, veterans, quality of life, mortality

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Introduction

Elderly individuals aged 65 years or older with chronic hepatitis C virus (HCV) infection are a large and growing population. The HCV prevalence rate in persons born between 1945 and 1965 is 3.5%, 5 times higher than that in other HCV-infected persons (AASLD/IDSA & HCV Panel, 2015). Furthermore, 75% of HCV-positive individuals are older than 65 years, and as many as 3.3% of adults living in long-term care settings have HCV infection (AASLD/IDSA & HCV Panel, 2015; Alvarez, Smaldone, & Larson, 2016). Successful treatment of HCV-infected elderly people may have a number of long-term health benefits, including slowed progression of liver disease and improved quality of life (Tseng et al., 2016; Younossi, Stepanova, Nader, & Henry, 2016). In a recent Veteran's Administration (VA) study of participants with a mean age of 60 to 63 years, successful treatment with direct-acting antiviral (DAA) regimens was associated with a reduction in all-cause mortality and incident hepatocellular carcinoma (Backus, Belperio, Shahoumian, & Mole, 2017).

Elbasvir (EBR)/grazoprevir (GZR) is an oral fixed-dose combination DAA treatment recently approved in the United States, Canada, Europe, and other countries for the treatment of HCV genotype (GT) 1 and GT4 infection (European Medicines Agency, 2016; Merck & Co., Inc., 2017). EBR, an NS5A inhibitor, and GZR, an NS3/4A

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protease inhibitor, have demonstrated high in vitro potency against most HCV genotypes (Asante-Appiah et al., 2017; Coburn et al., 2013; Harper et al., 2012; Lahser et al., 2016; Summa et al., 2012). Among treatment-naïve and treatment-experienced participants with HCV GT1 or GT4 monoinfection or HIV/HCV coinfection, a once-daily, 12-week regimen of EBR/GZR has consistently shown high rates of sustained virologic response (SVR) and was generally well tolerated (Jacobson et al., 2017; Kwo et al., 2016; Rockstroh et al., 2015; Roth et al., 2015; Zeuzem et al., 2015).

Elderly individuals who are receiving treatment for HCV infection may have frequent comorbidities, may be taking concomitant medications, or may have other age-related physiological changes such as declining renal function. In addition, compliance rates may vary in the elderly, and collectively, differences in comorbid conditions, concomitant medications, and age-related changes in drug metabolism or renal function may potentially impact the pharmacokinetics, efficacy, and tolerability of HCV therapies in this population. It is therefore important to evaluate the efficacy and safety of commonly used treatments for HCV infection, such as EBR/GZR, in an elderly population. The objective of this pooled integrated analysis was to determine the efficacy and safety of 12 weeks of EBR/GZR in individuals aged 65 years or older who were enrolled in Phase 2 or Phase 3 clinical trials.

Methods

This is an integrated retrospective analysis of pooled safety and efficacy data from 12 international Phase 2 and 3 clinical trials from the EBR/GZR clinical development program (Table 1). The detailed methodology and primary outcomes from these studies have been published or presented previously (C-WORTHY [NCT01717326, Protocol PN035], Lawitz et al., 2015; Sulkowski et al., 2015; C-SCAPE [NCT01932762, Protocol PN047], Brown et al., 2018; C-SURFER [NCT02092350, Protocol 052], Bruchfeld et al., 2017; Roth et al., 2015; Japanese participants [NCT02203149, Protocol PN058], Kumada et al., 2017; C-SALT [NCT02115321, Protocol PN059], Jacobson et al., 2015; C-EDGE Treatment-naïve [NCT02105467, Protocol PN060], Zeuzem et al., 2015; C-EDGE CO-INFECTION [NCT02105662, Protocol PN061], Rockstroh et al., 2015; C-EDGE CO-STAR [NCT02105688, Protocol PN062], Dore et al., 2016; C-EDGE Inherited Blood Disorders [NCT02252016, Protocol PN065], Hezode et al., 2017; C-CORAL [NCT02251990, Protocol PN067], Wei et al., 2017; C-EDGE Treatment-experienced [NCT02105701, Protocol PN068], Kwo et al., 2016; C-EDGE Head-2-Head [NCT02358044, Protocol PN077], Sperl et al., 2016). All studies were carried out in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practices, and local ethical and legal requirements. For each of these 12 clinical studies, independent institutional review boards or ethics committees reviewed and approved the protocol and applicable amendments for each participating institution. All participants provided voluntary written informed consent before trial entry. All studies included in this integrated analysis were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Participants

Participants with HCV GT1 or GT4 infection enrolled in previous Phase 2 or 3 clinical trials of EBR/GZR were included in this analysis. All participants were aged 18 years or older and had baseline HCV RNA ≥10,000 IU/mL. Participants were either treatment-naïve or had previously failed treatment with pegylated interferon–based HCV therapy. Individuals who had previously received treatment with a DAA-containing regimen were not included. The study population included participants with a number of different comorbidities including HIV coinfection (Rockstroh et al., 2015), advanced chronic kidney disease (CKD) (hemodialysis or CKD Stage 4/5) (Bruchfeld et al., 2017; Roth et al., 2015), and inherited blood disorders (hemophilia, sickle cell disease, or thalassemia) (Hezode et al., 2017), and participants receiving opiate agonist therapy (Dore et al., 2016). Participants were noncirrhotic or had Child–Turcott–Pugh (CTP) A cirrhosis defined as liver biopsy consistent with METAVIR F4 at any time prior to entry into the study; FibroScan >12.5 kPa within 12 months of study entry; or aspartate aminotransferase (AST)-to-platelet ratio >2.0 and FibroTest >0.75 within 12 months of study entry. Individuals with decompensated liver disease (presence or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs of advanced liver disease) or with evidence of hepatocellular carcinoma were excluded.

Treatment

All participants received EBR (50 mg/day)/GZR (100 mg/day) administered either as a fixed-dose combination tablet or as separate entities for 12 weeks. The primary end point in this pooled analysis was sustained virologic response 12 weeks after the end of therapy (SVR12), defined as HCV RNA less than the lower limit of quantification. HCV RNA was measured by COBAS® AmpliPrep/COBAS® Taqman® HCV test (v. 2.0). Efficacy and safety were analyzed according to participant age (≥65 years vs. <65 years).

Analyses

Efficacy analyses are based on the full analysis set (FAS) population, which included all participants who received at least one dose of study drug, and the modified FAS (mFAS) population, which excluded participants who

Table 1. Clinical Studies Included in the Integrated Analysis.

Study name (protocol number / clinical trials.gov identifier)	Participant population/HCV genotype	Participants aged <65 years (*n* = 2,139)	Participants aged ≥65 years (*n* = 339)	Total participants (*N* = 2,478)
C-WORTHY (PN035 / NCT01717326) (Lawitz et al., 2015; Sulkowski et al., 2015)	Cirrhotic and noncirrhotic, treatment-naïve, and treatment-experienced/GT1	124	11	135
C-SCAPE (PN047 / NCT01932762) (Brown et al., 2018)	Treatment-naïve/GT4	10	0	10
C-SURFER (PN052 / NCT02092350) (Roth et al., 2015)	CKD; treatment-naïve, cirrhotic, and noncirrhotic/GT1	187	37	224
Japan Phase 3 (PN058 / NCT02203149) (Kumada et al., 2017)	Japanese participants; cirrhotic and noncirrhotic, treatment-naïve, and treatment-experienced/GT1	199	167	366
C-SALT (PN059 / NCT02115321) (Jacobson et al., 2015)	Noncirrhotic, treatment-naïve, and treatment-experienced/GT1	8	2	10
C-EDGE Treatment-naïve (PN060 / NCT02105467) (Zeuzem et al., 2015)	Treatment-naïve/GT1 or GT4	360	46	406
C-EDGE CO-INFECTION (PN061 / NCT02105662) (Rockstroh et al., 2015)	HIV/HCV coinfected, HCV treatment-naïve/GT1 or GT4	210	6	216
C-EDGE CO-STAR (PN062 / NCT02105688) (Dore et al., 2016)	Treatment-naïve, on opioid agonist therapy/GT1 or GT4	284	3	287
C-EDGE-Inherited Blood Disorders (PN065 / NCT02252016) (Hezode et al., 2017)	Treatment-naïve and treatment-experienced/GT1 or GT4	150	5	155
C-CORAL (PN067 / NCT02251990) (Wei et al., 2017)	Asia-Pacific countries, treatment-naïve/GT1 or GT4	399	36	435
C-EDGE Treatment-Experienced (PN068 / NCT02105701) (Kwo et al., 2016)	Treatment-experienced participants/GT1 or GT4	88	17	105
C-EDGE Head-to-Head (PN077 / NCT02358044) (Sperl et al., 2016)	Treatment-naïve and treatment-experienced/GT1 or GT4	120	9	129

Note. HCV = hepatitis C virus; GT = genotype; CKD = chronic kidney disease; HIV = human immunodeficiency virus.

failed to achieve SVR12 for reasons unrelated to the treatment regimen or who had reinfection.

Results

Participant Demographics

A total of 2,139 participants aged <65 years and 339 participants aged ≥65 years were included in this analysis. Most demographic and baseline characteristics were similar between the two age groups; however, the proportion of Asian participants and those with HCV GT1b infection was lower among those aged <65 years compared with those aged ≥65 years (26% vs. 61% and 51% vs. 83%, respectively) (Table 2). Almost all participants aged ≥65 years had at least one medical history condition (334/339 [99%]), and the proportions of participants with hypertension, diabetes, and gastritis were lower in those aged <65 years compared with those aged ≥65 years. Fewer participants <65 years of age had platelets <100,000/μL compared with participants ≥65 years of age (15% vs. 54%).

Concomitant Medications

The proportion of participants receiving concomitant medications was lower among those aged <65 years than in those aged ≥65 years (83% vs. 95%) (Table 2). The most common concomitant medications were treatments for acid-related disorders (used by 19.7% of participants aged <65 years and 43.7% of those aged ≥65 years), agents acting on the renin-angiotensin system (17.4% in participants <65 years of age; 41.9% in those ≥65 years of age), agents acting on the hepatobiliary system (6.5% in participants <65 years of age; 37.2% in those ≥65 years of age), and calcium channel blockers (11.3% in <65 years of age; 32.7% in ≥65 years of age). The proportion of participants taking ursodiol was lower among those aged <65 years compared with those aged ≥65 years (6.1% vs. 36.6%).

Efficacy

Overall, the SVR12 rates in the FAS populations were 95.4% (2,041/2,139) in participants with HCV GT1 or

Table 2. Participant Demographics and Baseline Characteristics.

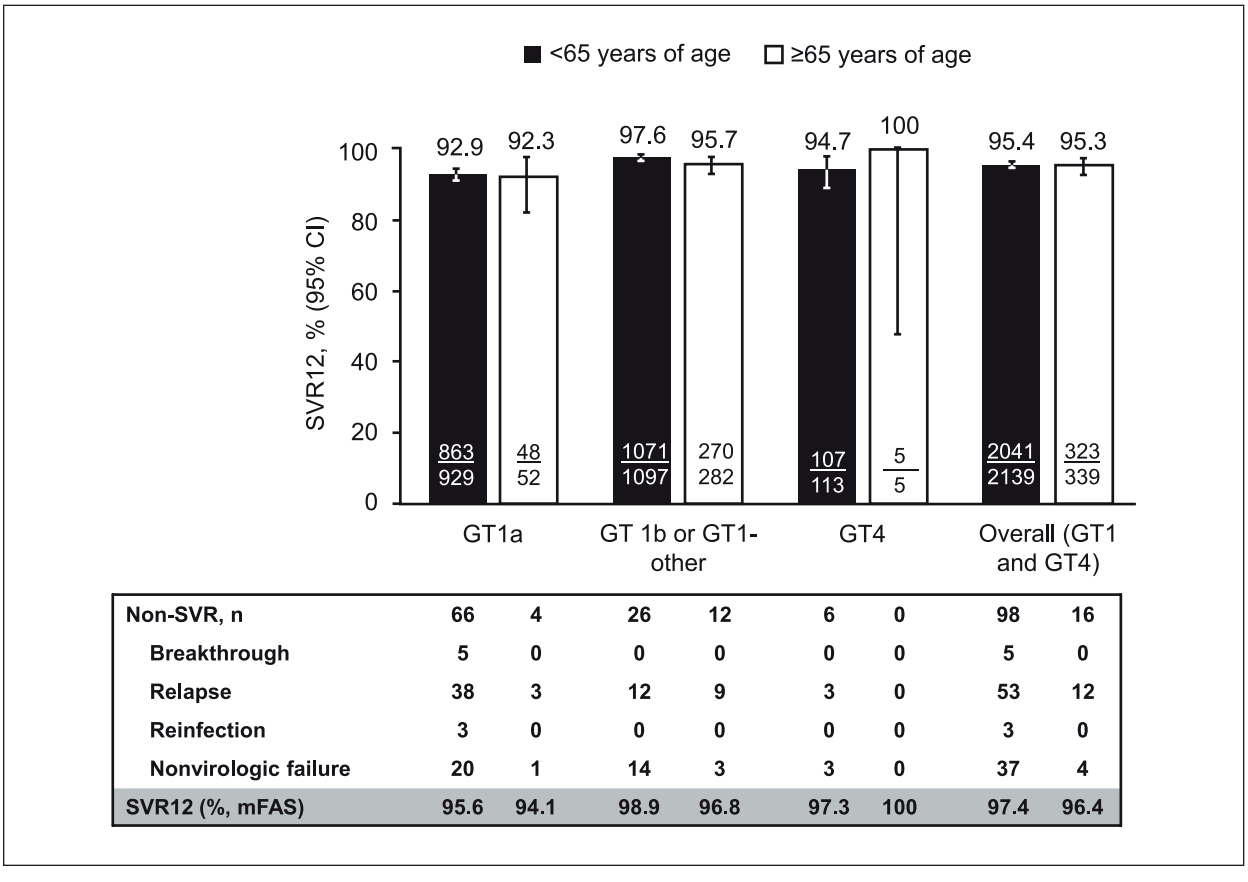
Characteristic	Participants aged <65 years (*n* = 2,139)	Participants aged ≥65 years (*n* = 339)
Sex, *n* (%)		
Male	1,307 (61)	149 (44)
Female	832 (39)	190 (56)
Age		
M (*SD*), years	48.8 (10.4)	69.9 (4.1)
Median (range), years	51 (18-64)	69 (65-82)
Race, *n* (%)		
White	1,264 (59)	89 (26)
Black or African American	278 (13)	39 (12)
Asian	564 (26)	208 (61)
Other or missing	33 (2)	3 (1)
Ethnicity, *n* (%)		
Non-Hispanic	1,979 (93)	331 (98)
Hispanic	129 (6)	8 (2)
HCV genotype and subtype, *n* (%)		
GT1	2,026 (95)	334 (99)
GT1a	929 (43)	52 (15)
GT1b or GT1-other[a]	1,097 (51)	282 (83)
GT4	113 (5)	5 (1)
HCV RNA, *n* (%)		
≤800,000 IU/mL	674 (32)	84 (25)
>800,000 IU/mL	1,465 (68)	255 (75)
≤2 million IU/mL	1,227 (57)	182 (54)
>2 million IU/mL	912 (43)	157 (46)
Geometric mean $\log_{10}$, IU/mL (*SD*)	6.1 (0.6)	6.2 (0.5)
Fibrosis stage, *n* (%)		
Cirrhosis	386 (18)	66 (19)
No cirrhosis	1,742 (81)	263 (78)
Unknown	11 (1)	10 (3)
Prior treatment, *n* (%)		
Treatment-naïve	1,812 (85)	243 (72)
Treatment-experienced	327 (15)	96 (28)
Body mass index, *n* (%)		
<30 kg/m²	1,824 (85)	299 (88)
≥30 kg/m²	315 (15)	40 (12)
M, kg/m², (*SD*)	25.5 (4.8)	24.6 (4.1)
Baseline eGFR[b], *n* (%)		
<30 mL/min/1.73 m^2	183 (9)	36 (11)
<60 to ≥30 mL/min/1.73 m^2	31 (1)	9 (3)
≥60 mL/min/1.73 m^2	1,923 (90)	294 (87)
Medical history conditions, *n* (%)		
One or more condition	1,956 (91)	334 (99)
Hypertension	556 (26)	194 (57)
Diabetes mellitus	135 (6)	43 (13)
Gastroesophageal reflux disease	212 (10)	60 (18)
Chronic gastritis	54 (3)	39 (12)
Baseline albumin, *n* (%)		
<3.5 g/dL	32 (1)	9 (3)
≥3.5 g/dL	2,107 (99)	330 (97)
M, g/dL (*SD*)	4.4 (0.4)	4.2 (0.3)
Baseline ALT, mean, IU/L (*SD*)	65.5 (54.5)	50.9 (39.4)
Baseline AST, mean, IU/L (*SD*)	54.8 (40.7)	51.6 (39.4)
Baseline total bilirubin, mean, mg/dL (*SD*)	0.61 (0.57)	0.61 (0.36)
Baseline platelets		
<100,000/μL	312 (15)	182 (54)
≥100,000/μL	1,822 (85)	156 (46)

(continued)

Table 2. (continued)

Characteristic	Participants aged <65 years (*n* = 2,139)	Participants aged ≥65 years (*n* = 339)
Unknown	5 (0.2)	1 (0.3)
Mean × 1000/μL	185.2 (90.4)	97.5 (89.9)
Concomitant medications,[c] *n* (%)		
Any	1,775 (83.0)	322 (95.0)
Drugs for acid-related disorders	422 (19.7)	148 (43.7)
Agents acting on the renin-angiotensin system	373 (17.4)	142 (41.9)
Agents acting on the hepatobiliary system[d]	140 (6.5)	126 (37.2)
Calcium channel blockers	242 (11.3)	111 (32.7)
Analgesics	681 (31.8)	107 (31.6)

Note. HCV = hepatitis C virus; GT = genotype; IU = international unit; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]GT1-other = 11 participants aged <65 years and 1 participant aged ≥65 years.
[b]eGFR = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).
[c]Incidence > 30% in either treatment group.
[d]Use of ursodiol: 130 (6.1%) in participants aged <65 years; 124 (36.6%) in participants aged ≥65 years.



Non-SVR, n	**66**	**4**	**26**	**12**	**6**	**0**	**98**	**16**
Breakthrough	**5**	**0**	**0**	**0**	**0**	**0**	**5**	**0**
Relapse	**38**	**3**	**12**	**9**	**3**	**0**	**53**	**12**
Reinfection	**3**	**0**	**0**	**0**	**0**	**0**	**3**	**0**
Nonvirologic failure	**20**	**1**	**14**	**3**	**3**	**0**	**37**	**4**
SVR12 (%, mFAS)	**95.6**	**94.1**	**98.9**	**96.8**	**97.3**	**100**	**97.4**	**96.4**

Figure 1. Efficacy rates in participants aged <65 years and ≥65 years (FAS).
Note. FAS = full analysis set; CI = confidence interval; SVR12 = sustained virologic response 12 weeks after the end of therapy; GT = genotype; mFAS = modified full analysis set.

GT4 infection aged <65 years and 95.3% (323/339) in those aged ≥65 years (Figure 1). Sixteen participants aged ≥65 years failed to achieve SVR12: 12 relapsed and four had nonvirologic failure.

Among the population with HCV GT1a infection, SVR12 was achieved by 92.9% (863/929) and 92.3% (48/52) of participants aged <65 years and ≥65 years, respectively. SVR12 rates in participants aged <65 and

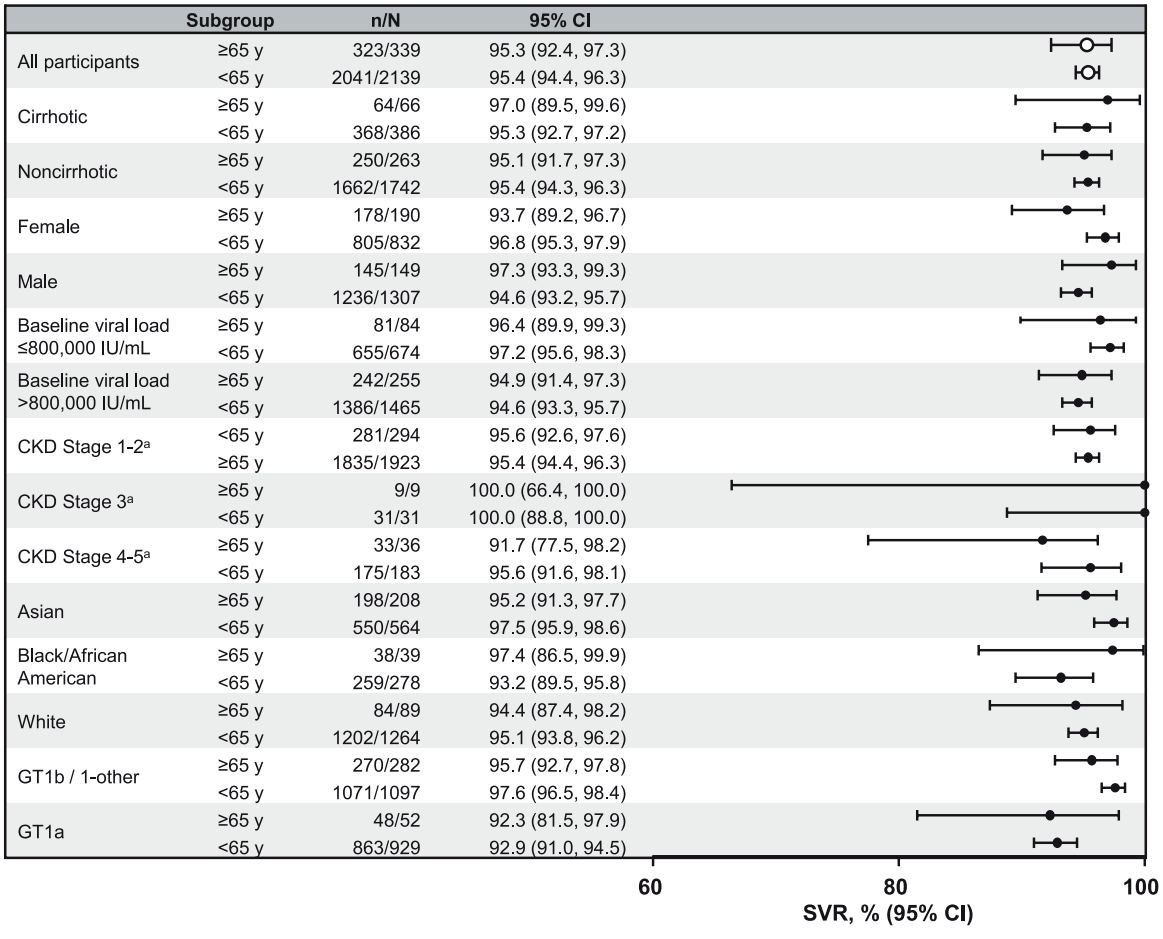


Figure 2. Efficacy rates in subgroups of participants.
Note. Stages 1 and 2 CKD were defined as eGFR ≥60 mL/min/1.73 m^2; Stage 3 CKD was defined as eGFR ≥30 to <60 mL/min/1.73 m^2; Stages 4 and 5 CKD were defined as eGFR <60 mL/min/1.73 m^2. CI = confidence interval; CKD = chronic kidney disease; GT = genotype; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus.
[a]eGFR was assessed using the Modification of Diet in Renal Disease–4 equation: eGFR (mL/min/1.73 m^2) = 175 × (Scr)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (conventional units, where Scr represents serum creatinine in mg/dL).

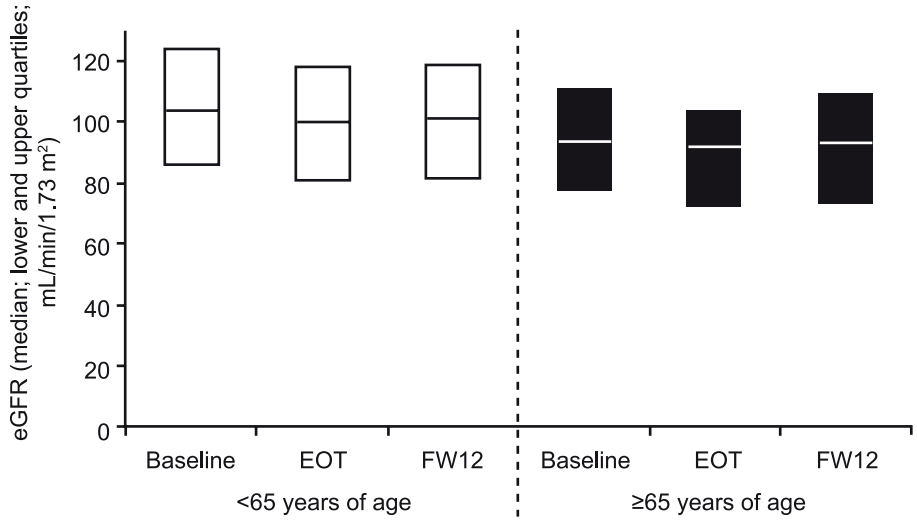
≥65 years were also similar in the populations with HCV GT1b/1-other infection (97.6% [1,071/1,097] and 95.7% [270/282]) and those with GT4 infection (94.7% [107/113] and 100% [5/5]). SVR12 rates were also similar in participants aged <65 years and those aged ≥65 years as well as across all other participant subgroups examined regardless of baseline viral load, estimated glomerular filtration rate (eGFR), race, HCV genotype, or the presence of cirrhosis (Figure 2).

Changes in eGFR Values

Among participants <65 years of age, the median eGFR values were 104.0 mL/min/1.73 m^2 at baseline, 100.4 mL/min/1.73 m^2 at end of treatment, and 101.1 mL/min/1.73 m^2 at 12 weeks after the end of treatment (follow-up week [FW] 12; Figure 3). Among participants ≥65 years of age, the median eGFR values were 97.7 mL/min/1.73 m^2 at baseline, 91.7 mL/min/1.73 m^2 at the end of treatment, and 93.8 mL/min/1.73 m^2 at FW12.

Tolerability

Serious adverse events (AEs) were reported in 68/2,139 (3.2%) of participants aged <65 years and 18/339 (5.3%) of those aged ≥65 years (Table 3). Discontinuations due to AEs were reported in 11/2,139 (0.5%) of participants aged <65 years and 5/339 (1.5%) of those aged ≥65 years. Drug-related serious AEs were also reported by 5 (0.2%) participants aged <65 years and by 1 participant (0.3%) aged ≥65 years (increased alanine aminotransferase [ALT] and AST levels). Three participants (0.1%) aged <65 years and one aged ≥65 years died (due to cardiac arrest considered not related to study medication in the participant aged ≥65 years). Commonly reported AEs (>5% in either group) were numerically lower in



Median eGFR, mL/min/1.73 m²	104.0	100.4	101.1	97.7	97.7	93.8
(Upper quartile, lower quartile)	(123.4, 86.4)	(118.0, 81.2)	(118.4, 81.9)	(111.0, 77.5)	(104.0, 72.0)	(109.6, 73.8)

Figure 3. Changes in eGFR from baseline to end of treatment to FW12 in participants aged <65 years and ≥65 years.
Note. eGFR = estimated glomerular filtration rate; FW = follow-up week; EOT = end of treatment.

Table 3. Tolerability of EBR/GZR in Participants Aged <65 and ≥65 Years.

Parameter	Participants aged <65 years (*n* = 2,139)	Participants aged ≥65 years (*n* = 339)
Any AE, *n* (%)	1,408 (65.8)	219 (64.6)
SAEs, *n* (%)	68 (3.2)	18 (5.3)
Drug-related SAEs, *n* (%)	5 (0.2)	1 (0.3)[a]
Discontinuations due to AEs, *n* (%)	11 (0.5)	5 (1.5)
Discontinuations due to drug-related AEs, *n* (%)	5 (0.2)	2 (0.6)[a]
Deaths, *n* (%)	3 (0.1)	1 (0.3)[b]
Common AEs[c]		
Headache	278 (13.0)	24 (7.1)
Fatigue	241 (11.3)	23 (6.8)
Nasopharyngitis	104 (4.9)	22 (6.5)
Nausea	153 (7.2)	14 (4.1)
Diarrhea	123 (5.8)	12 (3.5)
Laboratory findings, *n*/*N* (%)		
ALT: Grade 3: 5.1-10.0 × ULN	7/2,137 (0.3)	3/339 (0.9)
ALT: Grade 4: >10.0 × ULN	10/2,137 (0.5)	4/339 (1.2)
AST: Grade 3: 5.1-10.0 × ULN	8/2,137 (0.4)	4/339 (1.2)
AST: Grade 4: > 10.0 x ULN	4/2,137 (0.2)	2/339 (0.6)

Note. EBR = elbasvir; GZR = grazoprevir; AE = adverse event; SAE = severe adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
[a]Two participants discontinued due to drug-related increases in ALT and AST. One of these participants also had a drug-related SAE.
[b]One participant died due to cardiac arrest that was not considered to be drug-related.
[c]Common AEs > 5% in either group; not drug-related.

participants ≥65 years of age than in those <65 years of age (Table 3). Grade 4 ALT elevations were reported in 10 (0.5%) participants aged <65 years and in 4 (1.2%) of those aged ≥65 years. Grade 4 AST elevations were reported in 4 (0.2%) participants aged <65 years and in 2 (0.6%) participants aged ≥65 years.

Discussion

The clinical management of HCV infection in elderly individuals should take into account the important characteristics of this population. Elderly participants aged ≥65 years in this integrated analysis had a high proportion of comorbidities (99%). Most elderly participants (95%) were taking at least one concomitant medication, consistent with previous reports suggesting that elderly HCV-infected individuals have an increased risk of drug–drug interactions when treated with DAA regimens (Vermehren et al., 2016). Despite these special considerations in elderly individuals, rates of SVR12 were similar in participants aged <65 and those aged ≥65 years with HCV GT1 and GT4 infection receiving EBR/GZR for 12 weeks. Despite the higher frequency of comorbidities and concomitant medications, safety and tolerability observations from this analysis indicate a safety profile of EBR/GZR that is similar in both older and younger populations.

Consistent with the findings of the present analysis, other studies have also reported that treatment of HCV-infected persons aged ≥65 years with DAA regimens is safe and effective. In a retrospective analysis of clinical trial data in participants receiving ledipasvir/sofosbuvir with or without ribavirin for 8 to 24 weeks, SVR12 rates were similar in those aged ≥65 and those aged <65 years (98% vs. 97%), and all 24 participants aged ≥75 years also achieved SVR12 (Saab et al., 2016). In a real-world VA study of 17,487 participants with HCV GT1, 2, 3, or 4 infection receiving a VA-approved DAA regimen, SVR12 rates were 91.2%, 89.8%, 90.8%, 91.1%, 90.0%, and 93.8% in the subgroups aged <55 years, 55 to 59 years, 60 to 64 years, 65 to 69 years, 70 to 74 years, and >75 years of age, respectively (Su, Beste, Green, Berry, & Ioannou, 2017). Furthermore, age was not predictive of SVR in multivariate analysis after adjusting for baseline characteristics, either in the overall study population or in genotype-specific analyses (Su et al., 2017). In another real-world study of individuals with HCV infection and advanced fibrosis/cirrhosis, conducted in Italy, SVR12 rates in participants treated with DAAs were similar in those aged ≥65 years and those aged <65 years (94.7% vs. 90.5%) (Conti et al., 2017). In this analysis, among cirrhotic participants aged ≥65 years, SVR12 rates were lower in participants with a CTP score of CTP-B compared with those with a score of CTP-A (80.8% vs. 95.4%) and also lower in those with a Model for End-Stage Liver Disease (MELD) score ≥10 compared with those with a MELD score <10 (89.4% vs. 95.5%) (Conti et al., 2017). Finally, in another pooled analysis of clinical trial data, SVR12 rates were similar in participants receiving glecaprevir/pibrentasvir for 8 to 16 weeks aged ≥65 years and those aged <65 years (97.9% vs. 97.3%) (Foster, Kopecky-Bromberg, Lei, Trinh, & Mensa, 2017).

Although several studies have reported that treatment of individuals ≥65 years old with DAAs was generally safe, to our knowledge, no other study has examined the effects of treatment with DAA regimens on renal function in individuals with HCV infection aged ≥65 years. In this integrated retrospective analysis of participants ≥65 years of age receiving EBR/GZR for 12 weeks, we found that median eGFR values were similar at the end of treatment and at 12 weeks after the end of treatment compared with baseline. These observations are consistent with previous reports indicating that EBR/GZR does not worsen renal function in HCV-infected individuals with preexisting CKD Stage 3 or CKD Stage 4/5 (Reddy et al., 2017; Roth et al., 2015). Overall tolerability was also similar in the older and younger participant populations. The rates of AEs were similar in participants aged <65 years and in those aged ≥65 with respect to AEs, serious AEs, discontinuations due to AEs, discontinuations due to drug-related AEs, drug-related serious AEs, deaths, and common AEs. The safety of EBR/GZR in participants aged ≥65 years is reassuring considering that a high proportion of these participants had at least one comorbidity and were receiving at least one concomitant medication.

One limitation of this pooled analysis is the retrospective and nonrandomized nature of the study populations, resulting in notable differences in the demographics of the participants aged <65 years and ≥65 years. For example, the proportions of Asian participants and those with GT1b infection were higher among the older participant group than those aged <65 years. The proportion of female participants was also higher among those aged ≥65 years compared with those aged <65 years. Older participants also had a higher frequency of concomitant medical conditions and concomitant medications compared with younger participants. These differences in the study populations should be taken into consideration when making comparisons between the younger and older populations, although it is also noteworthy that in subgroup analyses, SVR12 rates were similar in Asian and HCV GT1b-infected participants aged ≥65 and <65 years.

These data indicate that advanced age should not be a barrier for initiating HCV treatment with DAAs such as EBR/GZR. Elderly HCV-infected individuals who achieve SVR12 have a reduced rate of progression to liver cirrhosis, improved quality of life, and overall significantly improved life expectancy compared with untreated age-matched individuals (Maor, Malnick, Melzer, & Leshno, 2016; Tseng et al., 2016; Younossi et al., 2016). Treatment of elderly individuals with chronic HCV infection with DAA regimens has been shown to be cost-effective (Ciaccio et al., 2017).

Conclusion

In this integrated analysis, the efficacy of 12 weeks of EBR/GZR was similar in HCV GT1- and GT4-infected participants aged 65 years or older and in participants younger than 65 years of age. EBR/GZR for 12 weeks

was safe and well tolerated in the participants aged 65 years or older.

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