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C-EDGE CO-STAR: Interim Results From the 3-year Follow-up Trial on Risk Factors and Rate of Reinfection in Patients on Opiate Agonist Therapy Previously Treated With Elbasvir/Grazoprevir for 12 Weeks

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Background

- Elbasvir (EBR)/grazoprevir (GZR) (**Figure 1**) is a fixed-dose combination tablet administered once daily, without regard to food intake, and is approved for the treatment of hepatitis C virus (HCV) genotype (GT)1 and 4 infections in a number of countries/regions, including the United States, Canada, and Europe
  - Retains in vitro activity against many clinically relevant resistance-associated variants[1-3]
  - Efficacious in treatment-naive and treatment-experienced compensated cirrhotic and non-cirrhotic patients with HCV, and in HIV/HCV co-infected patients[4-7]
  - Safety and efficacy demonstrated in special populations, including stage 4/5 chronic kidney disease and patients with inherited blood disorders[5,8]

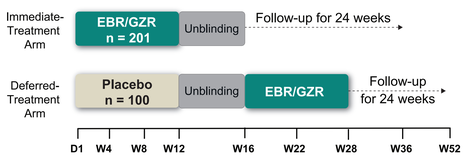
Figure 1. EBR/GZR

Patients and Methods

Study Design: Part A

- C-EDGE CO-STAR was a phase 3, randomized trial designed to evaluate EBR/GZR for 12 weeks in patients with HCV GT1, 4, or 6 infection on opiate agonist therapy (OAT) (**Figure 2**)
  - Patients were on OAT for at least 3 months, and consistently kept at least 80% of scheduled appointments while on OAT
  - Goal of having at least 20% of the patients with cirrhosis
  - Patients may be also co-infected with HIV
  - Urine drug screen was performed at each visit, but positive results did not exclude patients from the trial

Figure 2. Part A study design



D, day; W, week.

Study Design: Part B

- 3-year observational follow-up trial open to all patients who received at least one dose of EBR/GZR, with visits every 6 months to assess (**Figure 3**):
  - HCV RNA
    - Viral recurrence assumed to be reinfection, given the time between the end of treatment and time in observational follow-up; viral sequencing performed to compare samples at baseline and recurrence
    - HCV RNA determined with cobas® AmpliPrep/cobas® Taqman® HCV Test, v2.0®
    - Genotype determined by Abbott RealTime HCV Genotype II
  - Urine drug screen
  - Patient-reported behaviors
    - ACTIVATE Behavioral Questionnaire: patient-reported drug use

Figure 3. Part B study design

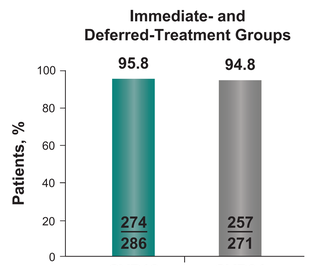
Next-generation sequencing performed on sequences at the NS3 and NS5A regions with ≈1% sensitivity threshold.
M, month.

Results

Part A

- High efficacy was observed, with sustained viral response at 12 weeks (SVR12) of 95.8% in the primary efficacy analysis population (**Figure 4**)
- Adherence was high, with 97% of patients demonstrating >95% adherence

Figure 4. SVR rates in Part A (modified full analysis set[1])



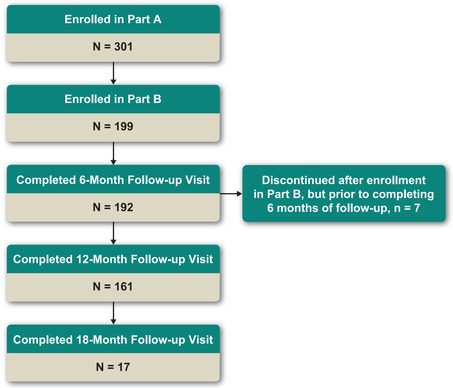
	SVR12	SVR24
Reinfection-counted as success	5	6
Failures		
Relapse	8	10
Breakthrough	2	2
Discontinuation	2	2

SVR24, sustained virologic response at 24 weeks.
[1]The primary efficacy analysis is the modified full analysis set, which excluded nonvirologic failures. In the full analysis set (where discontinuations were counted as failures), SVR12 was 91% and SVR24 was 85%.

Part B

- Results from enrollment and the 6-month follow-up visit are presented
- Patient disposition during Part B is shown in **Figure 5**

Figure 5. Patient disposition during Part B



- Patient demographics are shown in **Table 1**

Table 1. Patient demographics

	Patients enrolled in Part B (n = 199)	Patients not enrolled in Part B (n = 97)
Male, n (%)	151 (76)	76 (79)
Age, years, median (range)	48.6 (24-66)	44.1 (23-64)
Race, n (%)		
White	158 (79)	80 (82)
African American	31 (16)	6 (6)
Asian/other	10 (5)	11 (11)
HCV/HIV co-infected, n (%)	16 (8)	5 (5)
OAT at day 1 active treatment, n (%)		
Methadone	159 (80)	75 (77)
Buprenorphine	39 (20)	21 (22)
Genotype, n (%)		
1a	144 (72)	81 (84)
1b	39 (20)	5 (5)
4	14 (7)	4 (4)
6	2 (1)	7 (7)
Presence of cirrhosis (F4), n (%)	44 (22)	18 (19)
Positive urine drug screen at Part A enrollment, n (%)	112 (56)	66 (68)
Amphetamines	11 (6)	5 (5)
Benzodiazepines	43 (22)	34 (35)
Cannabinoids	45 (23)	42 (43)
Cocaine	20 (10)	10 (10)
Opiates	42 (21)	21 (22)

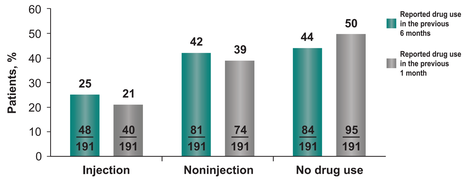
- Urine drug screen results are shown in **Table 2**

Table 2. Ongoing risk behavior: urine drug screen results

	Patients enrolled in Part B (n = 199)		
	Day 1 active treatment (Part A)	Enrollment in Part B	6-month follow-up
Number of patients with urine drug screen results	199	192	190
Any one positive urine drug screen result (excluding methadone and buprenorphine), %	56	59	59
Amphetamines	6	8	8
Benzodiazepines	22	23	23
Cannabinoids	23	26	28
Cocaine	10	11	11
Opiates	21	26	21

- 191 patients completed drug use behavior surveys, covering use in the previous 6 months or 1 month **(Figure 6)**

Figure 6. Reported drug use in previous 6 months or 1 month



Patients may have reported both injection and noninjection drug use.

- 36/40 patients who reported injecting any drug in the last month reported additional injection behaviors
  - Use of a new sterile needle and syringe
    - The majority of patients (81%, 29/36) reported for all injections
    - 17% (6/36) reported most of the time
    - 1 patient reported not using a clean needle or syringe
  - No patient reported using a needle and/or syringe after someone else had already used it
  - 42% (15/36) of patients mentioned using other injecting equipment after someone else, including spoons, drug solution mix, water or filters
  - Two patients reported that someone used a needle and/or syringe after they had used it

- 8 patients had recurrent viremia (**Table 3**)

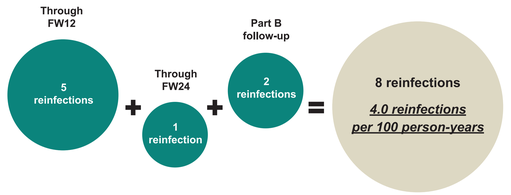
Table 3. Recurrent viremia

Demographics	Recurrent viremia time point	Outcome of viremia	Urine drug screen results	Reported risk factors at 6-month follow-up visit
48-year-old, noncirrhotic Asian male	FW8	Clearance	+ BZP at all visits	No reported drug use
33-year-old, noncirrhotic white female	FW8	Lost to follow-up	+AMP, OPA at TW12	Not enrolled in Part B
55-year-old, cirrhotic white female	FW8	Persistence	+BZP, OPA at all visits	Injecting heroin in the last month; no sharing of equipment
45-year-old, noncirrhotic Asian male	FW8	Clearance	+OPA at all visits +AMP at FW4	Not enrolled in Part B
37-year-old, noncirrhotic Asian female	FW8	Clearance	+AMP at all visits +BZP, OPA at TW12, FW4	Not enrolled in Part B
33-year-old, noncirrhotic white male	FW24	Persistence	negative	Injecting heroin in the last month; no sharing of equipment
56-year-old, noncirrhotic white male	Part B enrollment (7 months post-EOT)	Persistence	+AMP, BZP, OPA at FW12 and 6 month follow-up	Injecting heroin in the last month; sharing of spoons or mixing containers, water, and filter
53-year-old, noncirrhotic white male	6 months follow-up (12 months post-EOT)	Persistence	+BZP, OPA at FW24 and 6 month follow-up	No injecting of drugs reported; daily cannabis use

AMP, amphetamines; BZP, benzodiazepines; EOT, end of treatment; FW, follow-up week; OPA, opiates.

- Reinfections occurred at a rate of 2.8 per 100 person-years **(Figure 7)**

Figure 7. Incidence of reinfection

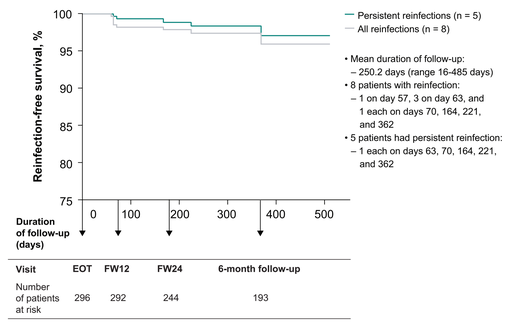


From End of Treatment Through Observation Visit 1		
8 reinfections	197.5 person-years	4.0 reinfections per 100 person-years (95% CI: 1.7, 8.0)
From End of Treatment Through Observation Visit 1 (Includes only those patients with persistent HCV RNA)		
5 reinfections	199.0 person-years	2.5 reinfections per 100 person-years (95% CI: 0.8, 5.9)

CI, confidence interval.

- The timeframe for reinfection is shown in **Figure 8**

Figure 8. Kaplan-Meier curve of time to HCV reinfection



- Mean duration of follow-up:
  - 250.2 days (range 16-485 days)
- 8 patients with reinfection:
  - 1 on day 57, 3 on day 63, and 1 each on days 70, 164, 221, and 362
- 5 patients had persistent reinfection:
  - 1 each on days 63, 70, 164, 221, and 362

Conclusions

- Patients enrolled in the long-term follow-up study were generally comparable to patients not enrolled in the long term follow-up study
- Based on urine drug screen data, drug use remained relatively stable from enrollment through 6 months of follow-up
- Injecting drug use was reported by 25% of patients in the last 6 months, and by 21% of patients in the last month
- Reinfection rate was higher in the immediate follow-up period through follow-up week (FW)12 compared with the time period through FW24 and through the ongoing observational follow-up
  - Overall reinfection rate through the 6-month follow-up period is 4.0/100 person-years (n = 8)
  - Including only those patients with persistence of viremia (n = 5), the effective reinfection rate is 2.5/100 person-years
- These data support addressing barriers in the treatment of patients on OAT and patients with ongoing drug use
- Follow-up will continue for a total of 36 months

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