C-EDGE CO-STAR: EFFICACY OF GRAZOPREVIR / ELBASVIR FIXED DOSE COMBINATION FOR 12 WEEKS IN HCV-INFECTED PERSONS WHO INJECT DRUGS ON OPIOID AGONIST THERAPY

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MY DISCLOSURES

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BACKGROUND AND AIM

- Injection drug use is the major risk factor for HCV epidemic in most high income countries, with people who inject drugs (PWID) accounting for 50-80% of HCV infections[1]
- Despite similar HCV treatment outcomes with IFN-containing therapy[2,3], PWID with current drug use have been excluded from IFN-free DAA development programs

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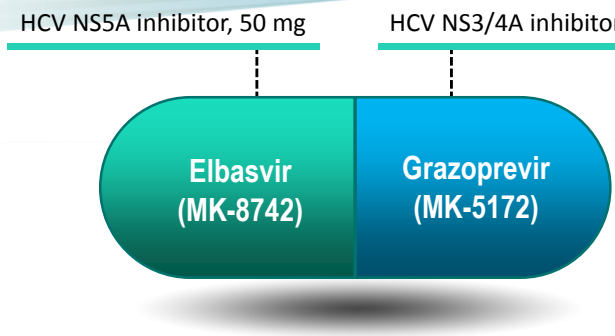
BACKGROUND



- Broad activity versus most HCV genotypes *in vitro*[1-3]
- Efficacious in treatment-naive & treatment-experienced patients, cirrhotic and non-cirrhotic patients, patients with HIV/HCV co-infection, and patients with end-stage kidney disease[4-6]

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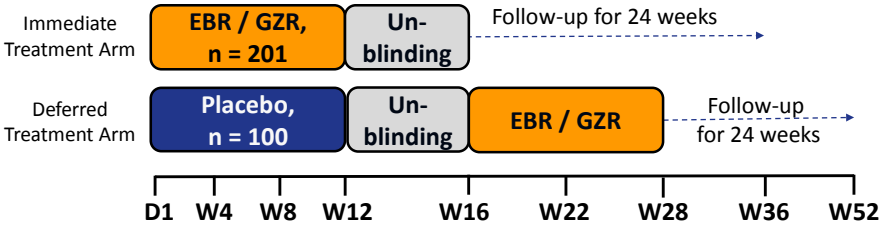
TRIAL DESIGN

- Phase 3, randomized, parallel-group, placebo-controlled, double-blind trial
- Treatment naïve, GT1, 4, 6; mixed genotypes of 1, 4, and 6 allowed
- On opiate agonist therapy (OAT) for at least 3 months, and consistently kept at least 80% of scheduled appointments while on OAT



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EFFICACY ANALYSES

- Endpoints
  - Primary endpoint: SVR12 (HCV RNA <15 IU/mL*)
  - Secondary endpoint: SVR24
- Analysis Population = Modified Full Analysis Set (mFAS)
  - Excludes patients who discontinued the trial for non-treatment related reasons (e.g., lost-to-follow-up and or discontinued due to reasons other than virologic failure)
  - Patients with data consistent with clearance of baseline infection and HCV RNA >15 IU/mL consistent with reinfection are counted as successes
- Virologic Analysis Methodology†
  - Comparison of samples at baseline and at viral recurrence
    - » Genotype
    - » Phylogenetic analysis
    - » Next generation / ultra deep sequencing

*HCV RNA determined with COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0®
†Genotype determined by Abbott RealTi*me* HCV Genotype II . Sequences analyzed for phylogenetic relationship using the software package MUSCLE , and alignment estimated using Maximum Likelihood phylogeny in the software package PhyML. Next generation sequencing performed on sequences at the NS3 and NS5A regions with ~1% sensitivity threshold.

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DEMOGRAPHICS

	Immediate treatment arm (n=201)	Deferred treatment arm (n=100)	Total (N=301)
	n (%)	n (%)	n (%)
Male	153 (76.1)	77 (77.0)	230 (76.4)
Age [median yrs; (range)]	48 (23-66)	47 (24-64)	48 (23-66)
Race			
White	158 (78.6)	84 (84.0)	242 (80.4)
African American	31 (15.4)	7 (7.0)	38 (12.6)
Asian/Other	12 (6.0)	9 (9.0)	21 (7.0)
Baseline HCV RNA (IU/mL)			
>2,000,000 IU/mL	114 (56.7)	51 (51.0)	165 (54.8)
HCV Genotype			
1a	154 (76.6)	75 (75.0)	229 (76.1)
1b	30 (14.9)	15 (15.0)	45 (15.0)
4	12 (6.0)	6 (6.0)	18 (6.0)
6	5 (2.5)	4 (4.0)	9 (3.0)
Cirrhosis			
Yes (F4)	40 (19.9)	22 (22.0)	62 (20.6)
HCV/HIV Co-infected	16 (8.0)	5 (5.0)	21 (7.0)
Urine drug screen (excluding opiate agonist therapy)			
positive at Day 1	122 (60.7)	52 (52.0)	174 (57.8)

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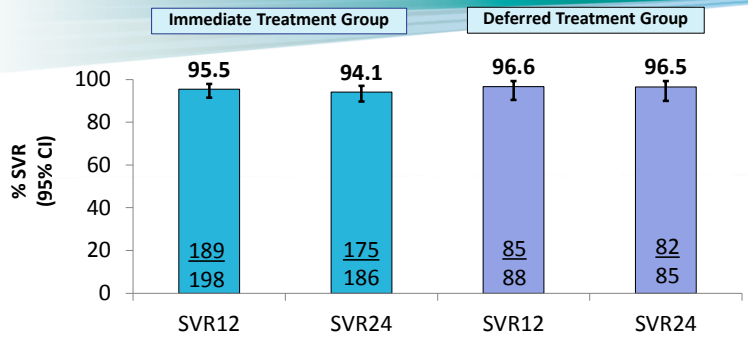
EFFICACY: SUSTAINED VIROLOGIC RESPONSE MODIFIED FULL ANALYSIS SET (mFAS)



Reinfection – counted as success	**5**	**5**	**0**	**1**
Failures				
Relapse	**7**	**9**	**1**	**1**
Breakthrough	**0**	**0**	**2**	**2**
Discontinuation	**2**	**2**	**0**	**0**

In the FAS (where discontinuations were counted as failures), SVR12 was 91.5% in the ITG and 85.6% in the DTG, SVR24 was 89.5% in the ITG and 85.3% in the DTG.

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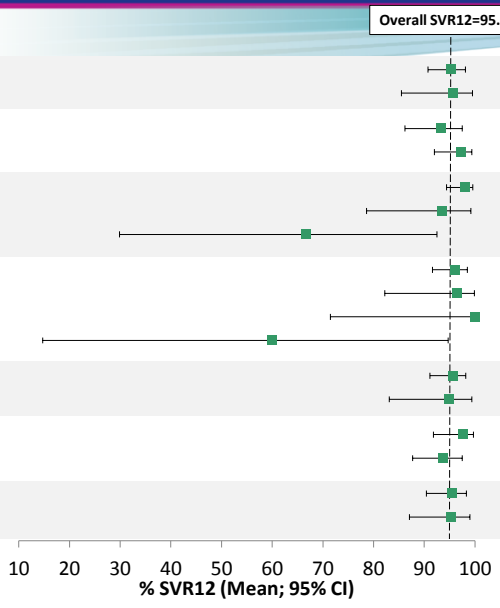
SVR12 IN THE IMMEDIATE TREATMENT GROUP: SUBGROUP ANALYSIS OF MODIFIED FULL ANALYSIS SET (mFAS)



Subgroup	n/m	SVR12 % (95% CI)
Male	144/151	95.4 (90.7, 98.1)
Female	45/47	95.7 (85.5, 99.5)
≥ 50 years	85/91	93.4 (86.2, 97.5)
< 50 years	104/107	97.2 (92.0, 99.4)
White	152/155	98.1 (94.4, 99.6)
African-American	29/31	93.5 (78.6, 99.2)
Asian	6/9	66.7 (29.9, 92.5)
GT1a	146/152	96.1 (91.6, 98.5)
GT1b	28/29	96.6 (82.2, 99.9)
GT4	11/11	100 (71.5, 100)
GT6	3/5	60.0 (14.7, 94.7)
Non-cirrhotic	151/158	95.6 (91.1, 98.2)
Cirrhotic	38/40	95.0 (83.1, 99.4)
HCV RNA ≤2 million	83/85	97.6 (91.8, 99.7)
HCV RNA >2 million	106/113	93.8 (87.7, 97.5)
Positive drug screen	127/133	95.5 (90.4, 98.3)
Negative drug screen	62/65	95.4 (87.1, 99.0)

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VIRAL RECURRENCE: PROBABLE REINFECTIONS

- In total, 6 patients were successfully treated for their baseline virus, but at the time of virologic failure had a different genotype, subtype, or viral strain detected
- 4/6 patients had a different genotype at viral recurrence compared to baseline
  - » The genotype found at viral recurrence was not amplified in any of the baseline samples using NGS / ultra deep sequencing and genotype specific primers.
- In all 6 cases, phylogenetic analysis of the nucleotide sequences support phylogenetically distinct viral strains at follow-up compared to baseline
- Following viral recurrence, 3 patients had undetectable HCV RNA without further treatment

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PROBABLE REINFECTIONS

Demographics	Fibrosis Stage	GT at Baseline	UDS at Baseline*	UDS at TW12*	Time point of detectable HCV RNA	GT at Follow-up
48 year-old Asian male	NC	1a	BZP, OPA	BZP	FW8	6a
33 year-old white female	NC	1a	- -	AMP, OPA	FW8	1a
55 year-old white female	C	1a	BZP, OPA	BZP, OPA	FW8	3a
45 year-old Asian male	NC	6a	- -	OPA	FW8	1b
37 year-old Asian female	NC	6a	AMP, BZP, OPA	AMP, BZP, OPA	FW8	6a
33 year-old white male	NC	1b	- -	- -	FW24	3a

*excludes opiate agonist therapy;
AMP=amphetamines; BZP=benzodiazepines; OPA=opiates; UDS = urine drug screen

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INCIDENCE OF REINFECTION

ITG From End of Treatment Through FW12:
• 5 reinfections out of 201 total patients • 47.4 person-years of follow-up • ***10.5 reinfections per 100 person years (95% CI: 3.4, 24.6)***
ITG and DTG From End of Treatment Through FW24:
• 6 reinfections out of 296 total patients (immediate and deferred treatment groups) • 130.6 person-years of follow-up • ***4.6 reinfections per 100 person years (95% CI: 1.7, 10.0)***

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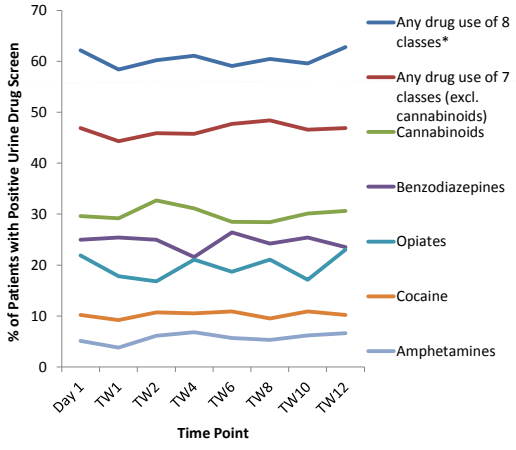
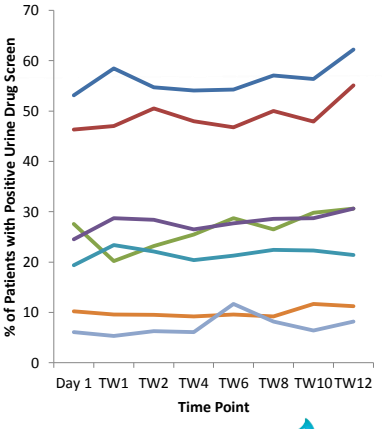
URINE DRUG SCREEN RESULTS

Immediate Treatment Arm; EBR/GZR Treatment Phase



Deferred Treatment Arm; Placebo Phase



* 8 drug classes: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, propoxyphene

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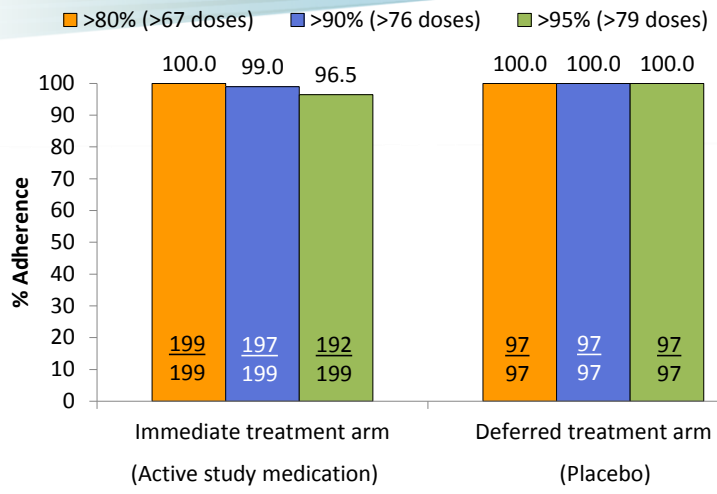
ADHERENCE



SAFETY DURING INITIAL TREATMENT PERIOD AND FIRST 14 DAYS OF FOLLOW-UP

	Immediate Treatment Arm (Active), n=201	Deferred Treatment Arm (Placebo), n=100	Total (n =301)
Serious AEs, n (%)	7 (3.5)	4 (4.0)	11 (3.7)
Serious Drug Related AEs, n (%)	1 (0.5)	1 (1.0)	2 (0.7)
Discontinuations, n (%)	1 (0.5)	1 (1.0)	2 (0.7)
Deaths, n (%)	0	1 (1.0)	1 (0.3)
Any AE, n (%)	167 (83.1)	83 (83.0)	250 (83.0)
Fatigue	32 (15.9)	20 (20.0)	52 (17.3)
Headache	25 (12.4)	13 (13.0)	38 (12.6)
Nausea	22 (10.9)	9 (9.0)	31 (10.3)
Diarrhea	19 (9.5)	9 (9.0)	28 (9.3)
Late ALT/AST > 5 x ULN, n (%)	0	0	0
Bilirubin >2.6 x ULN, n (%)	0	0	0
Hemoglobin <8.5 gm/dL, n (%)	0	1 (1.0)	1 (0.3)
Creatinine >2.5x baseline, n (%)	0	0	0

CONCLUSIONS

- EBR/GZR demonstrated high efficacy in GT1 and 4-infected patients receiving opiate agonist therapy
  - Limited by small number of GT6-infected patients
- Acceptable safety profile with comparable adverse event rates between the immediate- and deferred-treatment arms
- High study medication adherence
- Stable ongoing drug use throughout the initial treatment phase in both groups
- Data demonstrate support for treating HCV among subjects receiving OAT