

## C-EDGE CO-STAR: EFFICACY OF GRAZOPREVRIR / 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<sup>1</sup>
- Despite similar HCV treatment outcomes with IFN-containing therapy<sup>2,3</sup>, PWID with current drug use have been excluded from IFN-free DAA development programs

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## BACKGROUND

HCV NS5A inhibitor, 50 mg

HCV NS3/4A inhibitor, 100 mg

Elbasvir  
(MK-8742)

Grazoprevir  
(MK-5172)

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

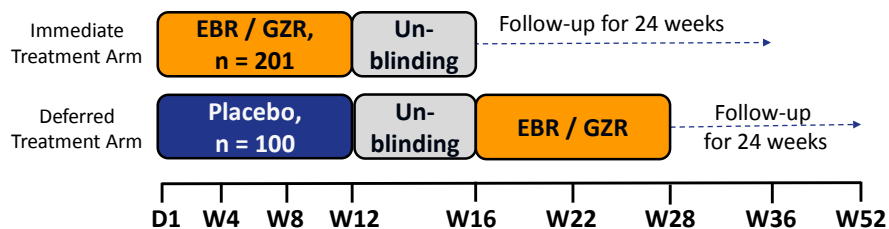
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## TRIAL DESIGN

- 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



## 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<sup>†</sup>
  - 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\*

<sup>†</sup>Genotype determined by Abbott RealTime 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.

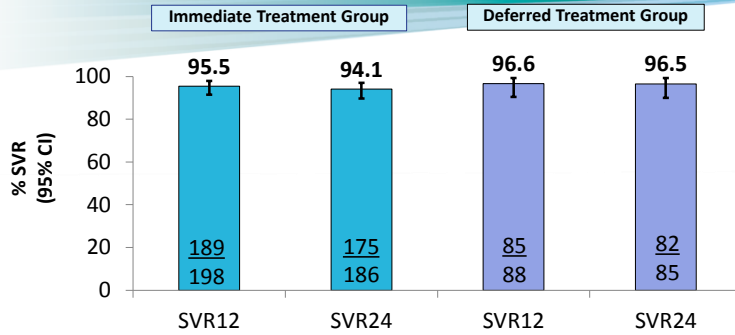


## DEMOGRAPHICS

	Immediate treatment arm (n=201)	Deferred treatment arm (n=100)	Total (N=301)
	n (%)	n (%)	n (%)
<b>Male</b>	153 (76.1)	77 (77.0)	230 (76.4)
<b>Age [median yrs; (range)]</b>	48 (23-66)	47 (24-64)	48 (23-66)
<b>Race</b>			
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)
<b>Baseline HCV RNA (IU/mL)</b>			
>2,000,000 IU/mL	114 (56.7)	51 (51.0)	165 (54.8)
<b>HCV Genotype</b>			
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)
<b>Cirrhosis</b>			
Yes (F4)	40 (19.9)	22 (22.0)	62 (20.6)
<b>HCV/HIV Co-infected</b>	16 (8.0)	5 (5.0)	21 (7.0)
<b>Urine drug screen (excluding opiate agonist therapy)</b>			
positive at Day 1	122 (60.7)	52 (52.0)	174 (57.8)



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

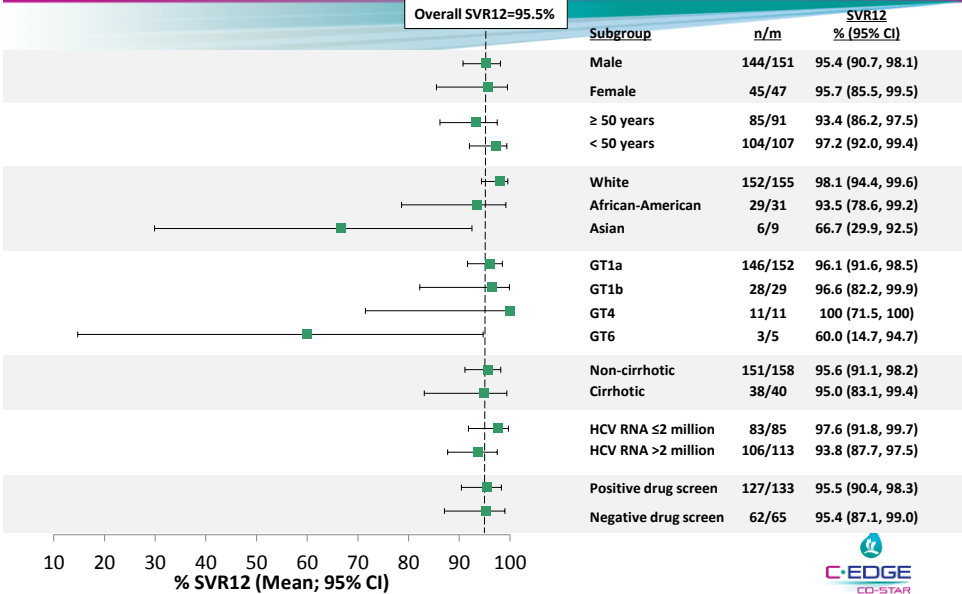


Reinfection – counted as success				
	5	5	0	1
Failures				
Relapse	7	9	1	1
Breakthrough	0	0	2	2
Discontinuation	2	2	0	0

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.



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



## 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



## 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



## INCIDENCE OF REINFECTION

### ITG From End of Treatment Through FW12:

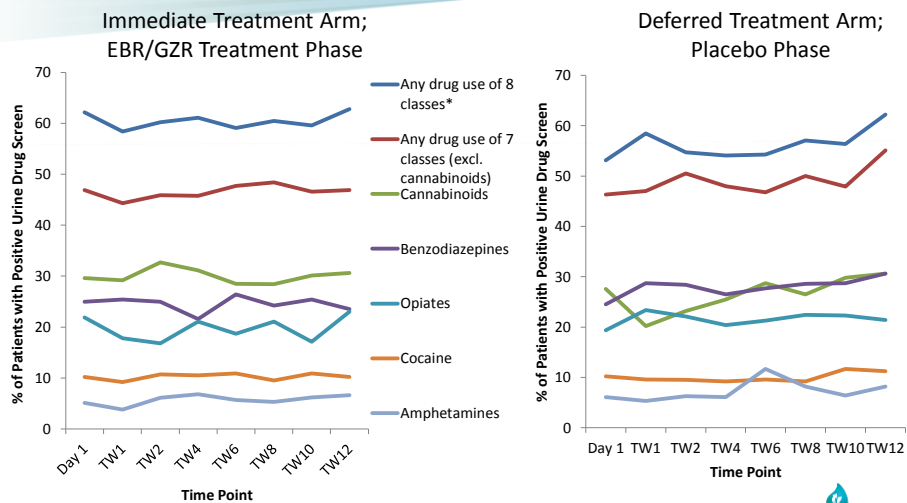
- 5 reinfections out of 201 total patients
- 47.4 person-years of follow-up
- **10.5 reinfections per 100 person years (95% CI: 3.4, 24.6)**

### 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)**



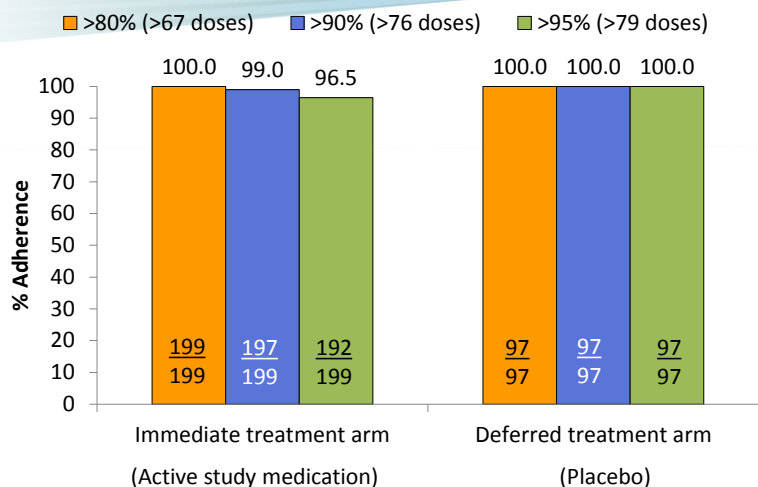
## URINE DRUG SCREEN RESULTS



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



## 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

