

DRUG-DRUG INTERACTIONS WITH GRAZOPREVIR/ELBASVIR: PRACTICAL CONSIDERATIONS FOR THE CARE OF HIV/HCV CO-INFECTED PATIENTS

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DISCLOSURE

- Employee of Merck & Co., Inc.
- Studies funded by Merck & Co., Inc.

BACKGROUND

Grazoprevir
(100 mg) Elbasvir
(50 mg)

- HCV NS3/4A inhibitor
- 100 mg once daily, oral



Grazoprevir
(MK-5172)

- HCV NS5A inhibitor
- 50 mg once daily, oral



Elbasvir
(MK-8742)

- Broad *in vitro* activity against most HCV genotypes¹⁻³
- Retains *in vitro* activity against many clinically relevant resistance associated variants (RAVs)¹⁻³
- All-oral, once-daily, one tablet, fixed-dose combination regimen

1. Summa V, et al. *Antimicrobial Agent Chemother* 2012;56;4161-67
2. Coburn CA, et al. *ChemMedChem* 2013; 8: 1930-40
3. Harper S, et al. *ACS Med Chem Lett.* 2012 Mar 2;3(4):332-6.

GRAZOPREVIR/ELBASVIR: RELEVANT METABOLISM AND TRANSPORTER PROPERTIES

Grazoprevir
(100 mg) Elbasvir
(50 mg)

- **GRAZOPREVIR (GZR)**
 - **Metabolism**
 - CYP3A/P-gp substrate
 - Weak CYP3A inhibitor (34% ↑ in midazolam)
 - **Transporters**
 - Substrate of Organic Anion-Transporting Polypeptides (OATP)1B
 - Inhibitor of intestinal Breast Cancer Resistance Protein (BCRP)
(oral abstract #17)
- **ELBASVIR (EBR)**
 - **Metabolism**
 - CYP3A/P-gp substrate
 - **Transporters**
 - Inhibitor of intestinal BCRP (oral abstract #17)
 - Minimal P-gp inhibition

BACKGROUND

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(50 mg)

- HCV infection is a leading cause of morbidity and mortality among patients with HIV-1¹⁻³
 - rapid progression of liver disease
 - increased risk of cirrhosis, end-stage liver disease, and HCC^{4,5}
 - Treatment of HCV infection in the coinfecting population represents an important unmet medical need
- Since medications to treat HIV/HCV concurrently may give rise to clinically significant drug-drug interactions, it is important to evaluate the potential for these interactions to inform coadministration of HIV ART with HCV DAA in co-infected patients

1. Monga HK, et al. *Clin Infect Dis* 2001;33(2):240-247. 2. Konerman MA, et al. *Hepatology* 2014;59(3):767-775
3. Pinchoff J, et al. *Clin Infect Dis* 2014;58(8):1047-1054. 4. Lo Re V, III, et al. *Ann Intern Med* 2014;160(6):369-379.
5. Rockstroh JK, et al. *J Hepatol* 2013;59(2):213-220.

GZR/EBR DDI RESULTS WITH COMMONLY USED HIV ART

Grazoprevir (100 mg) Elbasvir (50 mg)

HIV ARV	Effect on GZR AUC	Effect on EBR AUC	Effect on Interacting Drug AUC	Recommendation
tenofovir disoproxil fumarate	↔ 0.9x	↔ 0.9x	↑1.2x with GZR ↑1.3x with EBR	No adjustment
raltegravir	↔ 0.9x	↔ 1.0x	↑1.4x with GZR ↔1.0x with EBR	No adjustment
dolutegravir	↔ 1.0x	↔ 1.0x	↑1.2x with GZR+EBR	No adjustment
#63 rilpivirine	↔ 0.9x	↔ 1.1x	↔ 1.1x with GZR+EBR	No adjustment
efavirenz	↓ 0.2x	↓ 0.5x	↔ 1.0x with GZR ↓0.8x with EBR	Not recommended
darunavir/ritonavir	↑ 7.5x	↑ 1.7x	↔1.1x with GZR ↔1.0x with EBR	Not recommended
atazanavir/ritonavir	↑ 10.6x	↑ 4.8x	↑1.4x with GZR ↔1.1x with EBR	Not recommended
lopinavir/ritonavir	↑ 12.9x	↑ 3.7x	↔1.0x with GZR ↔1.0x with EBR	Not recommended

COMMONLY USED HIV ART THAT ARE EXPECTED TO HAVE NO DDI WITH GZR/EBR

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- No DDI study with abacavir, lamivudine, emtricitabine, but no expected DDI= **no dose adjustments**
 - ABC, 3TC, FTC not expected to inhibit or induce any relevant metabolic enzymes or transporters of GZR and EBR
 - GZR and EBR are unlikely to alter the PK of ABC, 3TC, FTC since they are renally cleared
- No DDI study with etravirine (moderate CYP3A inducer), but etravirine is expected to decrease GZR and EBR exposures based on efavirenz DDI results= **not recommended**
- No DDI study with other HIV PIs, but unboosted atazanavir, saquinavir/r, tipranavir/r are expected to significantly increase GZR exposures via OATP1B inhibition= **not recommended**

C-EDGE CO-INFECTED: PHASE 3 STUDY OF GRAZOPREVRIR / ELBASVIR IN PATIENTS WITH HCV/HIV

*Jürgen K. Rockstroh, Mark Nelson, Christine Katlama, Jay Lalezari,
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Heather L. Platt, Michael Robertson, Mark Sulkowski*



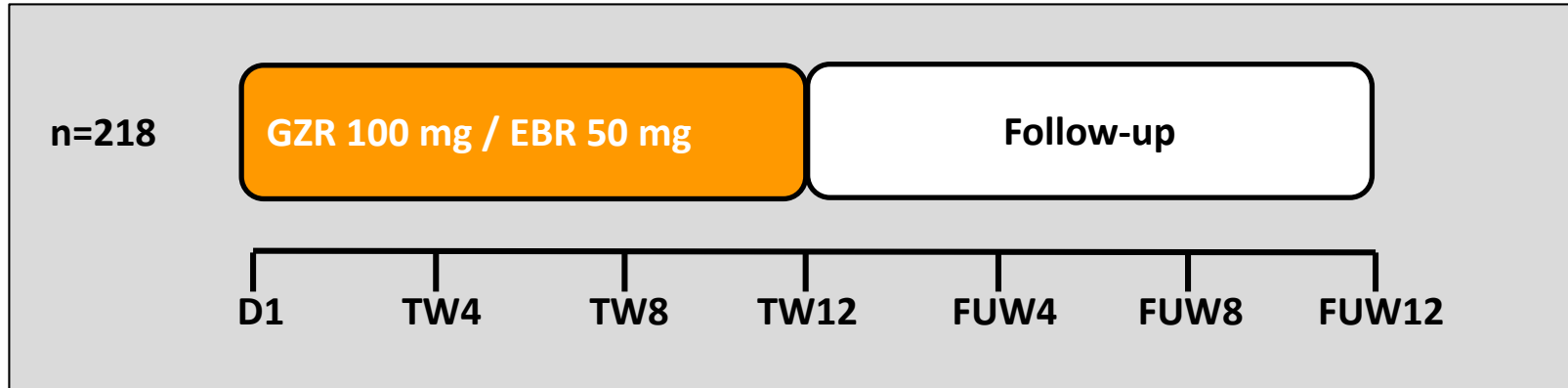
Presented at EASL 2015, *J Hepatol* 2015;62 (supp. 2): S675



C·EDGE
CO-INFECTION

STUDY DESIGN

Grazoprevir
(100 mg) Elbasvir
(50 mg)



- An open-label, single-arm, multicenter study across Europe, US and Australia
- Primary endpoint: SVR12 (HCV RNA <15 IU/mL*)
- HCV treatment-naive patients with HCV GT1, 4 or 6 infection with or without cirrhosis
- Co-infected with HIV-1:
 - Naive to ART with CD4+ >500 cells/mm³ and HIV RNA <50,000 copies/mL
 - On stable on ART for ≥8 weeks and CD4+ >200 cells/mm³ and undetectable HIV RNA
 - Stable antiretroviral therapy (ART) included TDF or abacavir, and either 3TC or FTC plus raltegravir, dolutegravir, or rilpivirine

*COBAS TaqMan v2.0 [LLOQ <15 IU/mL]

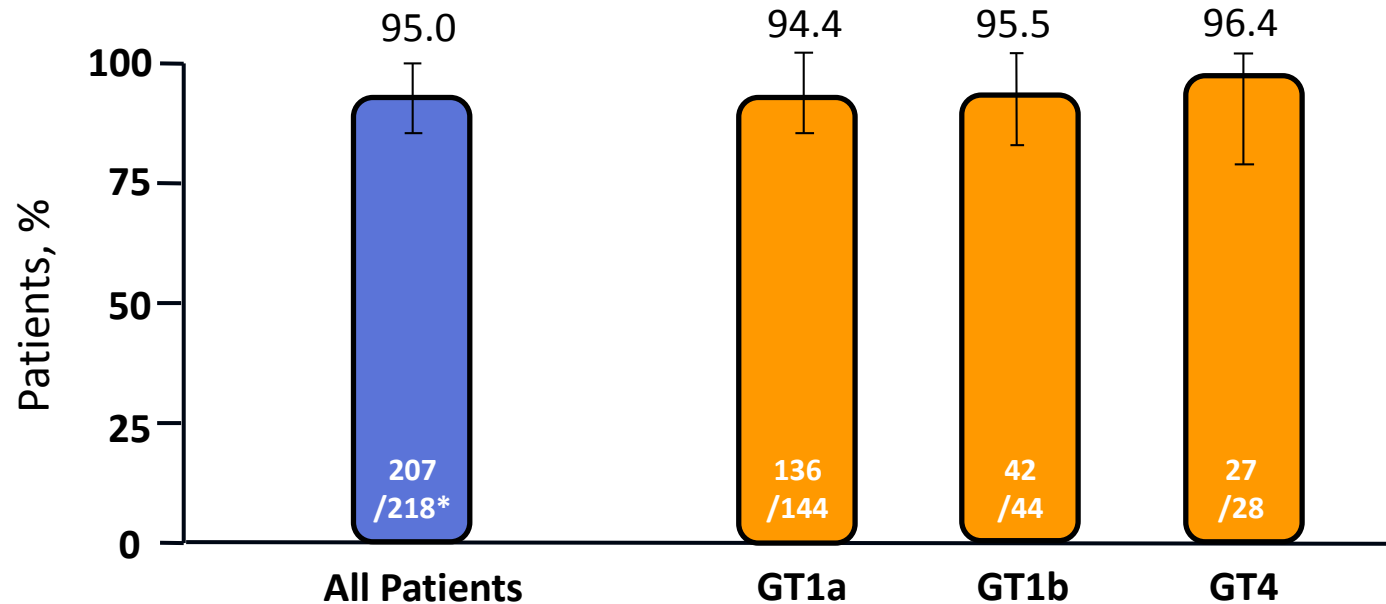
DEMOGRAPHICS: HIV DISEASE

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	All Patients N = 218
Antiretroviral therapy, n (%)	
Receiving ART with undetectable HIV RNA	211 (96.8)
Naïve to ART	7 (3.2)
Baseline CD4 count (cells/ μ L)	
Mean (SD)	613 (0.57)
Median (1 st quartile – 3 rd quartile)	568 (424-766)
Antiretroviral therapy, n (%)	
Abacavir containing regimen	47 (21.6)
Tenofovir containing regimen	164 (75.2)
Raltegravir	113 (51.8)
Dolutegravir	59 (27.1)
Rilpivirine	38 (17.4)

SVR12 – FULL ANALYSIS SET

Grazoprevir (100 mg) Elbasvir (50 mg)



LTFU or discontinued unrelated to VF	4	3	1	0
Breakthrough	0	0	0	0
Relapse	6	4	1	1
Reinfection	1	1	0	0

*1 patient with GT6 infection and 1 patient with GT1 not-otherwise subtyped were also included; both patients achieved SVR12.

GT = genotype; LTFU = lost to follow-up

ADVERSE EVENTS

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Patients with:	All Patients N = 218
Serious AE, n (%)	6* (2.8)
Serious drug-related AE, n (%)	0 (0)
Discontinuation due to AE, n (%)	0 (0)
Deaths, n (%)	0 (0)
Any adverse event [†] , n (%)	167 (76.6)
Fatigue	29 (13.3)
Headache	27 (12.4)
Nausea	20 (9.2)
Late ALT or AST >5.0 x ULN [‡] , n (%)	2 (0.9)
Lowest hemoglobin on treatment, n (%)	
≥8.5 to <10 g/dL	1 (0.5)
Elevation of total bilirubin [¶] , n (%)	
>2.5 – 5.0 × baseline	8 (3.7)
>5.0 × baseline	1 (0.5)
Creatinine >2.5 x baseline, n (%)	0 (0)

*2 SAEs were reported during the treatment period (convulsion and pneumonia) and 4 SAEs were reported during follow-up (erysipelas; acute psychosis and urinary retention; ulnar fracture; and spontaneous bacterial peritonitis)

[†]All AEs, regardless of relationship to study drug reported in >5% of patients.

[‡]ALT/AST >5× ULN after TW4 with an ALT/AST ≤ ULN between TW2 and TW4

[¶]Bilirubin elevations were not associated with simultaneous ALT increases

SUMMARY OF GRAZOPREVRIR AND ELBASVIR METABOLISM

Grazoprevir
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(50 mg)

- Other drugs may affect pharmacokinetics of grazoprevir (a substrate of CYP3A/P-gp and OATP1B) and elbasvir (CYP3A/P-gp substrate)
 - CYP3A/P-gp inhibitors may be coadministered with GZR/EBR
 - Coadministration with CYP3A/P-gp inducers with GZR/EBR is not recommended
 - Coadministration of OATP1B inhibitors with GZR is not recommended
- GZR and EBR are intestinal BCRP inhibitors*
 - Dosing recommendations for specific statins that are BCRP substrates when coadministered with GZR/EBR

*Caro et al., IWCPHHT 2015, oral abstract #17

SUMMARY OF GRAZOPREVIR AND ELBASVIR IN HIV/HCV CO-INFECTED PATIENTS

Grazoprevir
(100 mg) Elbasvir
(50 mg)

- High rates of SVR were achieved with excellent safety profile in patients with HCV GT1, 4 and 6 and HIV co-infection receiving the all-oral FDC of GZR / EBR
- Current DDI guidance for treatment of HIV/HCV co-infection:
 - HIV NRTI (TDF, 3TC, FTC, ABC) may be coadministered with GZR/EBR without dose adjustment
 - HIV Integrase Inhibitors (raltegravir, dolutegravir) may be coadministered with GZR/EBR without dose adjustment
 - HIV NNRTI rilpivirine may be coadministered with GZR/EBR without dose adjustment
 - Moderate/strong CYP3A/P-gp inducers (including efavirenz and etravirine) are not recommended for coadministration, since they decrease or is expected to decrease GZR and EBR concentrations
 - HIV protease inhibitors are not recommended for coadministration, since they increase or are expected to increase GZR and EBR concentrations

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