CO-ADMINISTRATION WITH GRAZOPREVIR AND ELBASVIR HAS NO EFFECT ON PRAVASTATIN EXPOSURE BUT INCREASES ROSUVASTATIN EXPOSURE IN HEALTHY SUBJECTS

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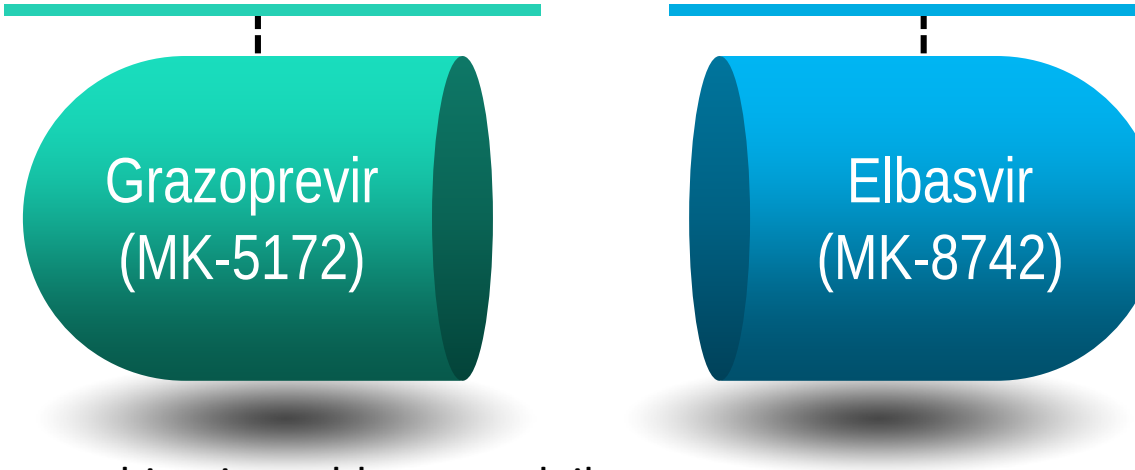
DISCLOSURES

- Employee of Merck & Co.

GRAZOPREVIR (GZR) + ELBASVIR (EBR)

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

- HCV NS5A inhibitor
- 50 mg once daily, oral



- Fixed-dose combination tablet once daily
- Broad activity against most HCV genotypes *in vitro*[1-2]
- Efficacious in many sub-population of HCV patients: treatment-naïve & treatment-experienced, cirrhotic & non-cirrhotic, chronic kidney disease, HIV/HCV co-infected[3-7]

1. Brown A, et al. C-SCAPE. EASL. 2015; Abstract P0771.
2. Kwo P, et al. C-EDGE. EASL. 2015; Abstract P0886
3. Zeuzem S, et al. Ann Intern Med. 2015; doi: 10.7326/M15-0785
4. Rockstroh JK, et al. C-EDGE. EASL. 2015; Abstract P0887.
5. Poordad F, et al. C-SWIFT. EASL. 2015; Abstract O006.
6. Monsour Jr H, et al. C-SURFER. EASL. 2015; Abstract LP02.
7. Jacobson IM, et al. C-SALT Part A. EASL. 2015; Abstract O008.

BACKGROUND & OBJECTIVES

- **Background:** Many HCV-infected patients also have hypertension, hypercholesterolemia, and heart disease for which HMG-CoA reductase inhibitors are widely prescribed

- **Objective:** Evaluate the effect of coadministration of either rosuvastatin or pravastatin with GZR and EBR

- **Previous Statin DDI studies:**
  - No clinically-relevant DDI between GZR and pitavastatin
  - Clinically-relevant increase in atorvastatin exposure when coadministered with GZR; proposed dose of atorvastatin limited to 20 mg daily

POTENTIAL FOR DRUG INTERACTIONS BETWEEN ROSUVASTATIN OR PRAVASTATIN AND GZR & EBR

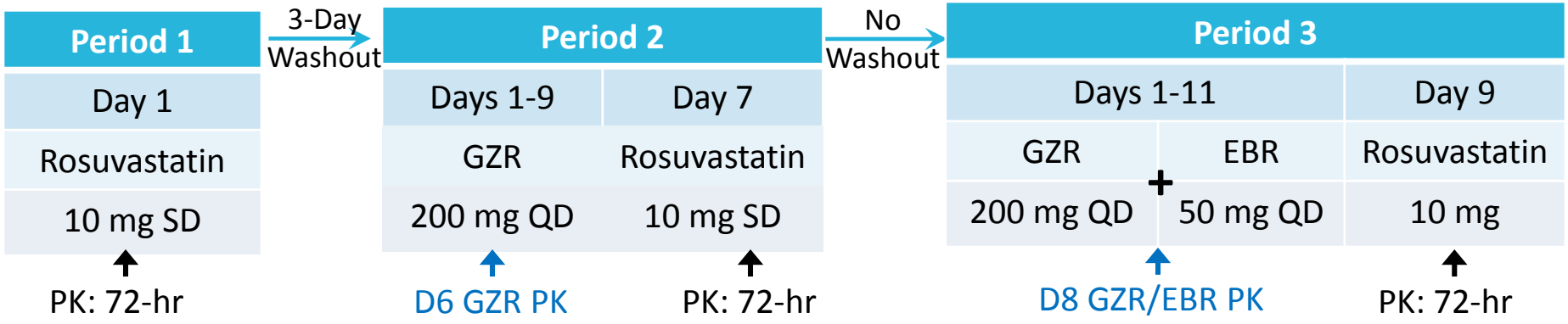
- **Grazoprevir and elbasvir :**
  - GZR and EBR are CYP3A/P-gp substrates, GZR is OATP1B substrate
  - Not inhibitors of OATP1B hepatic uptake transporters
  - Potential intestinal inhibition of BCRP efflux transporters based on in vitro data
  - GZR is a weak CYP3A inhibitor (based on 35% increase in midazolam exposure)
- **Rosuvastatin**
  - Substrate of OATP1B and BCRP transporters, CYP2C9 substrate
  - Not anticipated to inhibit/induce GZR or EBR metabolic enzymes or transporters
  - ➢ *GZR+EBR may increase rosuvastatin exposure via intestinal BCRP inhibition*
  - ➢ *No changes in GZR or EBR concentrations anticipated*
- **Pravastatin**
  - OATP1B substrate (renal is major elimination pathway), minor CYP3A metabolism
  - Not anticipated to inhibit/induce GZR or EBR metabolic enzymes or transporters
  - ➢ *GZR may have minor increase in pravastatin exposure via weak CYP3A inhibition*
  - ➢ *No changes in GZR or EBR concentrations anticipated*

STUDY DESIGN

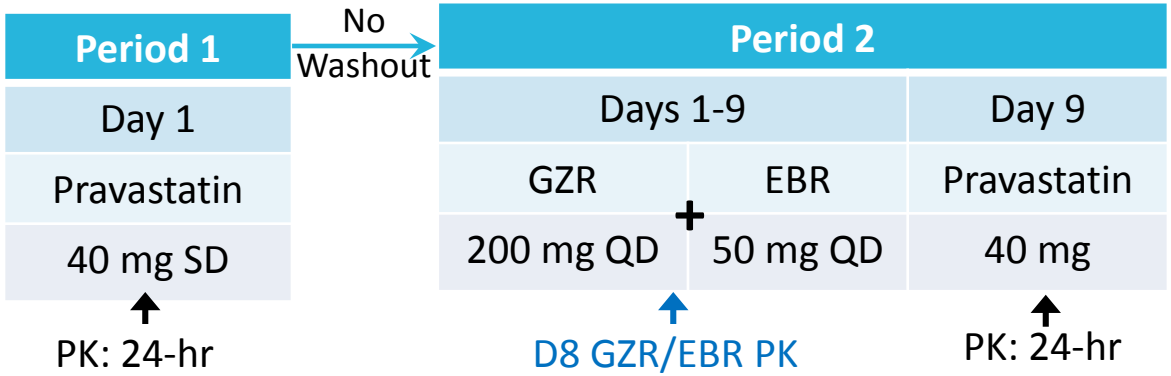
Grazoprevir (100 mg) + Elbasvir (50 mg)

- Open label, 2-part, 12 healthy males/female subjects/part, ages 19-55 years
- Individual GZR and EBR tablets (not FDC)
- 200 mg GZR in healthy subjects to match 100 mg GZR exposure in HCV patients

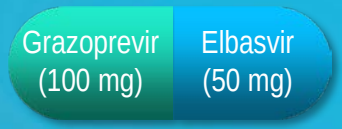
Rosuvastatin DDI:



Pravastatin DDI:



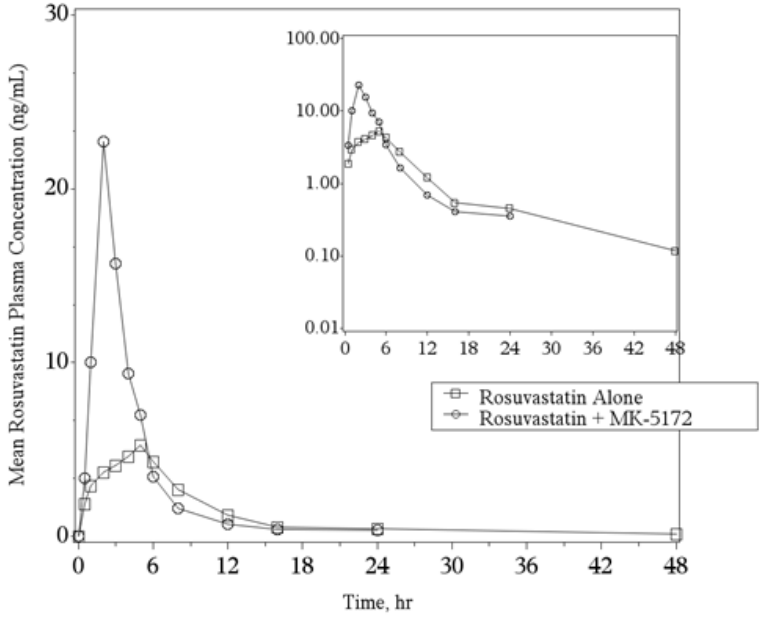
SAFETY



- No SAEs
- 1 discontinuation for lab AE
  - increased creatinine phosphokinase (CPK) unrelated to study drug
- GZR and EBR were well tolerated

PK RESULTS: ROSUVASTATIN + GZR

Grazoprevir (100 mg) Elbasvir (50 mg)



- Rosuvastatin increase greater for Cmax (4.25) than AUC (1.85) when coadministered with GZR
  - Suggests increased rosuvastatin absorption due to inhibition of intestinal BCRP efflux by GZR
- No meaningful effect on GZR PK, as anticipated

Rosuvastatin PK Parameter	Rosuvastatin + GZR/ Rosuvastatin Alone	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	1.85	(1.56, 2.19)
C_{max}‡ (ng/mL)	4.25	(3.25, 5.56)
C_{24}‡ (ng/mL)	0.80	(0.70, 0.91)

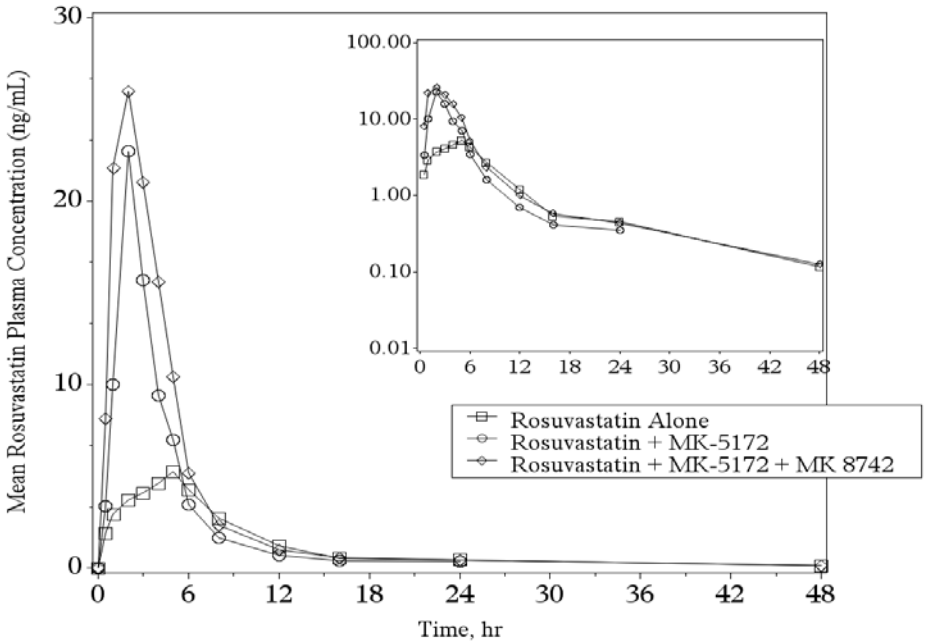
‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

GZR PK Parameter	Rosuvastatin + GZR/ GZR Alone	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	1.16	(0.94, 1.44)
C_{max}‡ (ng/mL)	1.13	(0.77, 1.65)
C_{24}‡ (ng/mL)	0.93	(0.84, 1.03)

‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

PK RESULTS: ROSUVASTATIN + GZR+EBR

Grazoprevir (100 mg) Elbasvir (50 mg)



Rosuvastatin PK Parameter	Rosuvastatin + GZR + EBR/ Rosuvastatin Alone	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	2.68	(2.26, 3.17)
C_{max}‡ (ng/mL)	5.49	(4.29, 7.04)
C_{24}‡ (ng/mL)	0.98	(0.84, 1.13)

‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

- Rosuvastatin increase greater for Cmax (5.49) than AUC (2.68) when co-administered with GZR+EBR
  - Suggests increased absorption due to GZR+EBR inhibition of intestinal BCRP efflux
- Rosuvastatin increase slightly greater with GZR+EBR than GZR alone
  - Possibly additional (smaller) effect of co-administration of EBR with GZR on intestinal BCRP inhibition

PK RESULTS: ROSUVASTATIN + GZR+EBR

- No statistically significant effect on GZR or EBR when coadministered with rosuvastatin

GZR PK Parameter	Rosuvastatin + GZR + EBR/ GZR + EBR	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	**1.01**	(0.79, 1.28)
C_{max}‡ (ng/mL)	**0.97**	(0.63, 1.50)
C_{24}‡ (ng/mL)	**0.95**	(0.87, 1.04)

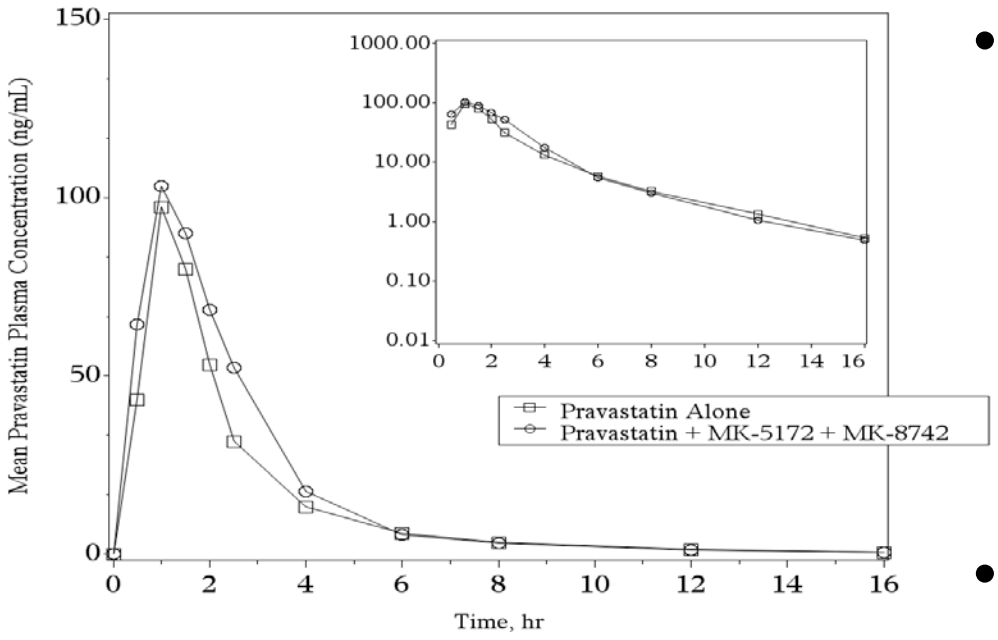
‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

EBR PK Parameter	Rosuvastatin + GZR + EBR/ GZR +EBR	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	**1.09**	(0.98, 1.21)
C_{max}‡ (ng/mL)	**1.11**	(0.99, 1.26)
C_{24}‡ (ng/mL)	**0.96**	(0.86, 1.08)

‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

PK RESULTS: PRAVASTATIN + GZR + EBR

Grazoprevir (100 mg) Elbasvir (50 mg)



Pravastatin PK Parameter	Pravastatin + GZR + EBR/ Pravastatin Alone	
	GMR	90% CI
AUC_{0-24}‡ (ng/mL·hr)	**1.28**	(1.08, 1.51)
C_{max}‡ (ng/mL)	**1.28**	(1.05, 1.55)

‡Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log transformed values.

- GZR+EBR coadministration resulted in 28% ↑ in pravastatin AUC and Cmax, which is not clinically-relevant
  - Consistent with weak CYP3A inhibition by GZR
- No meaningful effect on GZR or EBR, as anticipated

ROSUVASTATIN & PRAVASTATIN DDI SUMMARY

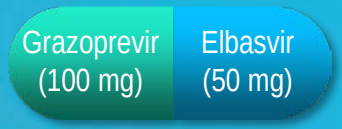
- GZR and EBR were safe and well-tolerated when co-administered with rosuvastatin and pravastatin

- ROSUVASTATIN PK:
  - Coadministered with GZR+EBR resulted in 2.7-fold ↑ AUC, 5.5-fold ↑ Cmax
  - Results suggest both GZR and EBR inhibit intestinal BCRP efflux

- PRAVASTATIN PK:
  - No clinically-relevant drug-drug interaction when co-administered with GZR+EBR

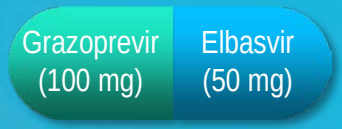
- GZR & EBR PK:
  - Steady-state exposure not meaningfully altered by co-administration with rosuvastatin or pravastatin

CONCLUSIONS



- PROPOSED STATIN DOSING RECOMMENDATIONS WHEN CO-ADMINISTERED WITH GZR+EBR:
  - Pravastatin: May be coadministered without dose adjustment
  - Rosuvastatin: Do not exceed a daily dose of 10 mg
  - Pitavastatin (previous study): May be coadministered without dose adjustment
  - Atorvastatin (previous study): Do not exceed a daily dose of 20 mg
- Pravastatin, up to 10 mg daily of rosuvastatin, and up to 20 mg daily of atorvastatin were administered in Phase 2/3 studies and are currently safe and well-tolerated

ACKNOWLEDGEMENTS



- Subjects for their participation and investigators and clinical site staff for conduct of the study
- Merck study team