A CLINICALLY MEANINGFUL DRUG-DRUG INTERACTION OBSERVED BETWEEN ZEPATIER™ (GRAZOPREVIR/ELBASVIR) AND STRIBILD® HIV FIXED-DOSE COMBINATION IN HEALTHY SUBJECTS

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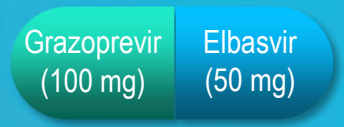
DISCLOSURES

- Employee of Merck & Co.

BACKGROUND: ZEPATIER™



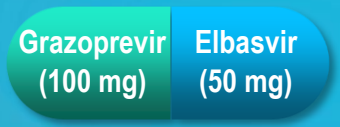
- HCV NS3/4A inhibitor
- 100 mg once daily, oral

- HCV NS5A inhibitor
- 50 mg once daily, oral

- 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]
- Fixed-dose combination tablet once daily

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 AND OBJECTIVE



Background

- 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 HCV/HIV co-infected patients

Objective

- Evaluate the effect of coadministration of Stribild® with Zepatier™ on the PK of individual components of Stribild® and Zepatier™

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POTENTIAL FOR DRUG INTERACTIONS BETWEEN ZEPATIER™ AND STRIBILD®

- **Grazoprevir and elbasvir :**
  - GZR and EBR: CYP3A/P-gp substrates; GZR: OATP1B substrate
  - Not inhibitors of UGT1A1, OATP1B hepatic uptake transporters or OAT1, OAT3, and OCT2 renal transporters, not inducers of CYP3A
  - Intestinal inhibitors of BCRP
  - GZR is a weak CYP3A inhibitor (based on 35% increase in midazolam exposure)
- **Elvitegravir (EVG)**
  - Substrate of CYP3A (major) and UGT1A1/3
  - Not anticipated to meaningfully inhibit/induce GZR or EBR metabolic enzymes or transporters
- **Emtricitabine (FTC)**
  - Not significantly metabolized, renal is major elimination pathway
  - Not anticipated to inhibit/induce GZR or EBR metabolic enzymes or transporters
- **Tenofovir disoproxil fumarate (TDF) and tenofovir (TFV)**
  - TDF is a substrate for BCRP and P-gp; TDF and TFV are not CYP substrates
  - TFV renally eliminated (glomerular filtration and tubular secretion)
- **Cobicistat (COBI)**
  - Substrate of CYP3A and CYP2D6
  - Inhibitor of CYP3A and P-gp, OATP1B1/3 and BCRP

POTENTIAL FOR DRUG INTERACTIONS BETWEEN ZEPATIER™ AND STRIBILD® (CONTINUED)

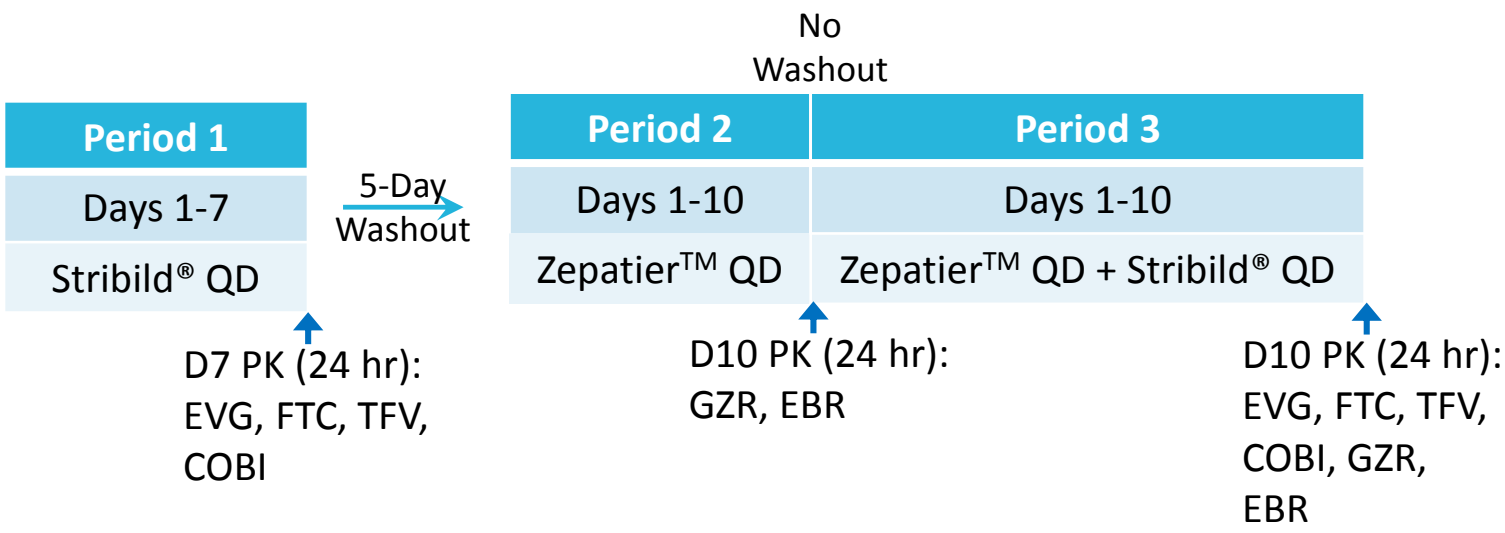
- Zepatier™ and Stribild® co-administration
  - Effect on Stribild® components:
    - *Is not expected to affect FTC concentration*
    - *May increase EVG and COBI concentration via CYP3A inhibition*
    - *May increase TFV concentration via intestinal BCRP and P-gp inhibition*[1]
  - Effect on ZEPATIER™ components:
    - *May increase GZR concentration via CYP3A and OATP1B1 inhibition*
    - *May increase EBR concentration via CYP3A inhibition*

1. Poster abstract P_56

STUDY DESIGN

Grazoprevir (100 mg) Elbasvir (50 mg)

- Open-label, 22 healthy males/female subjects, ages 19-53 years
- Zepatier™ FDC tablets (100 mg GZR/50 mg EBR)
- Stribild FDC tablets (150 mg EVG/200 mg FTC/300 mg TDF/150 mg COBI)

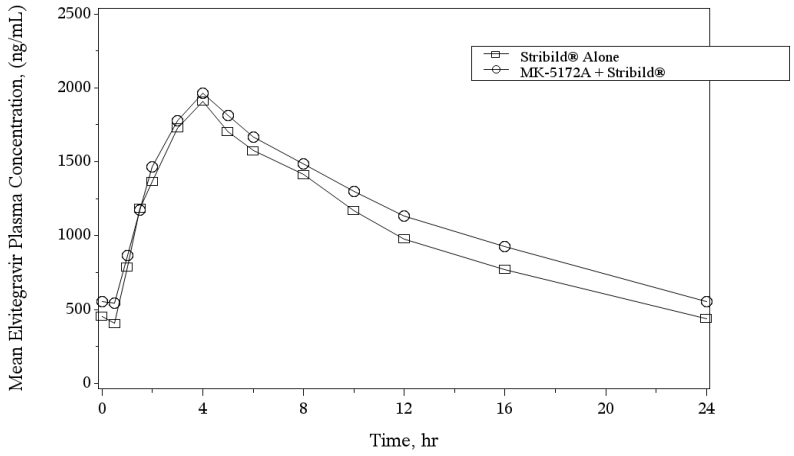


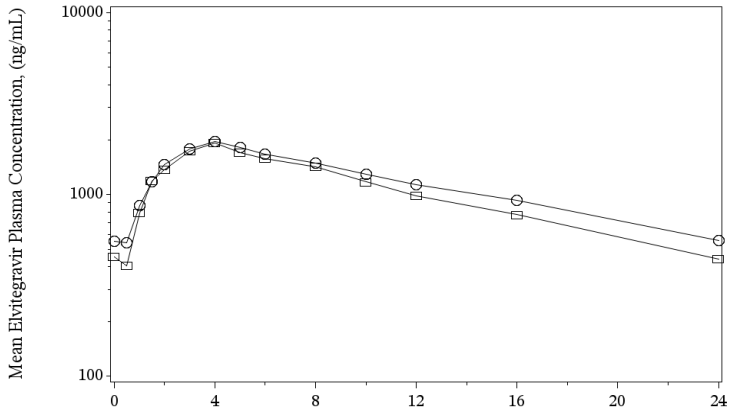
SAFETY AND TOLERABILITY

- The administration of multiple oral doses of Stribild® alone, Zepatier™ alone, and Stribild® + Zepatier™ were generally well tolerated in healthy males and females
- The most common AEs were:
  - **Stribild® alone**: headache, nausea , myalgia, nasal congestion, and throat irritation
  - **Zepatier™ alone**: headache
  - **Zepatier™ + Stribild®**: nausea and eructation
- All AEs were mild in intensity, were transient in nature, and resolved by study conclusion
- No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or ECGs as a function of treatment

PK RESULTS: ELVITEGRAVIR

Grazoprevir (100 mg) | Elbasvir (50 mg)





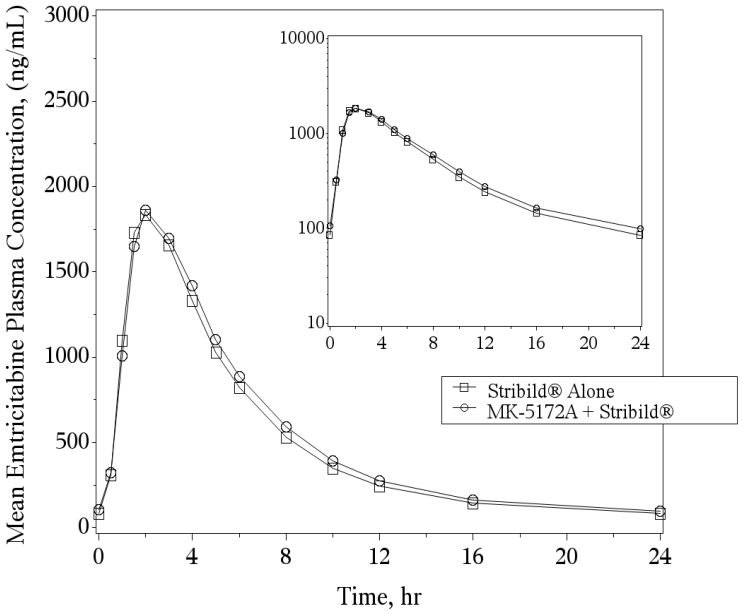
Elvitegravir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Stribild® Alone	
	GMR	90% CI
AUC_{0-24} ‡	1.10	(1.00, 1.21)
C_{max} ‡	1.02	(0.93, 1.11)
C_{24} ‡	1.31	(1.11, 1.55)

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

- Zepatier™ and Stribild® co-administration has no clinically meaningful effect on steady state elvitegravir exposure

PK RESULTS: EMTRICITABINE

Grazoprevir (100 mg) | Elbasvir (50 mg)



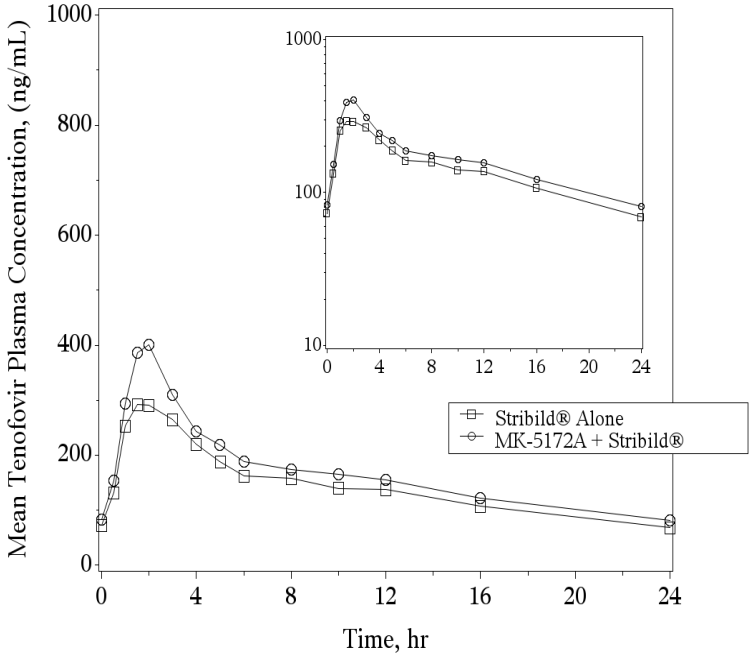
Emtricitabine Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Stribild® Alone	
	GMR	90% CI
AUC_{0-24} ‡	1.07	(1.03, 1.10)
C_{max} ‡	0.96	(0.90, 1.02)
C_{24} ‡	1.19	(1.13, 1.25)

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

- Zepatier™ and Stribild® co-administration has no clinically meaningful effect on steady state emtricitabine exposure

PK RESULTS: TENOFOVIR

Grazoprevir (100 mg) Elbasvir (50 mg)



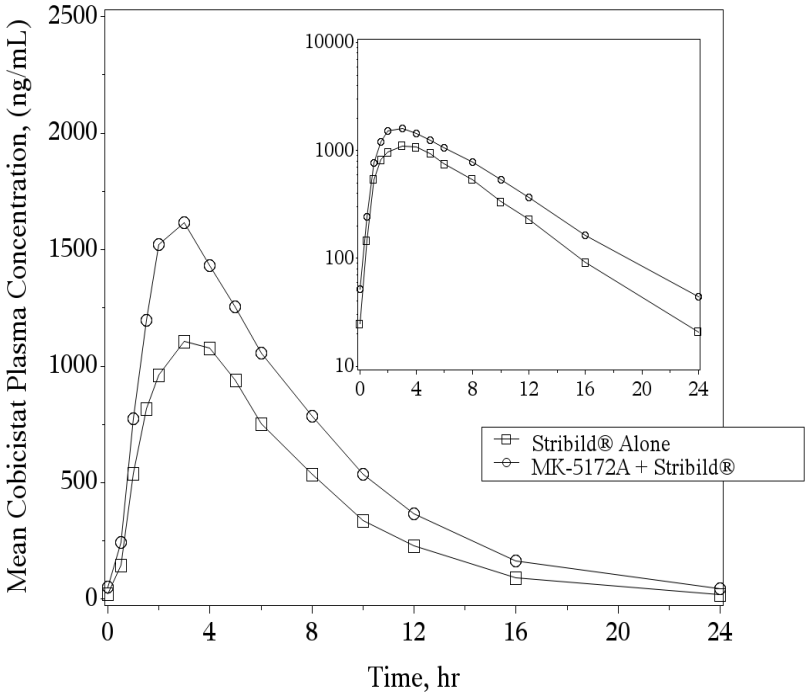
Tenofovir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Stribild® Alone	
	GMR	90% CI
AUC_{0-24} ‡	1.18	(1.13, 1.24)
C_{max} ‡	1.25	(1.14, 1.37)
C_{24} ‡	1.20	(1.15, 1.26)

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

- Zepatier™ and Stribild® co-administration slightly increases steady state tenofovir exposure via intestinal BCRP inhibition

PK RESULTS: COBICISTAT

Grazoprevir (100 mg) Elbasvir (50 mg)



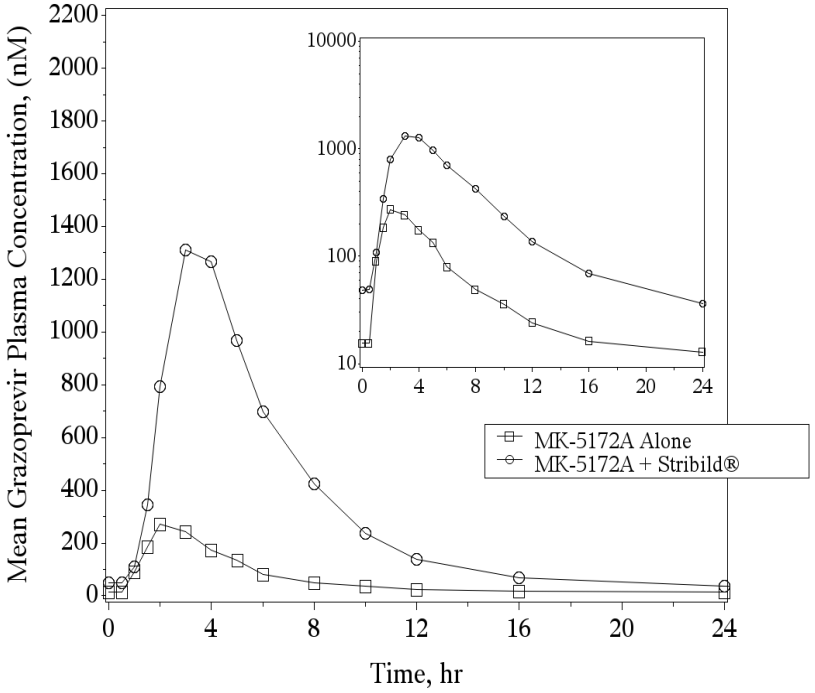
Cobicistat Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Stribild® Alone	
	GMR	90% CI
AUC_{0-24} ‡	1.49	(1.42, 1.57)
C_{max} ‡	1.39	(1.29, 1.50)

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

- Zepatier™ and Stribild® co-administration increases steady state cobicistat exposure via CYP3A inhibition by GZR

PK RESULTS: GRAZOPREVIR

Grazoprevir (100 mg) | Elbasvir (50 mg)



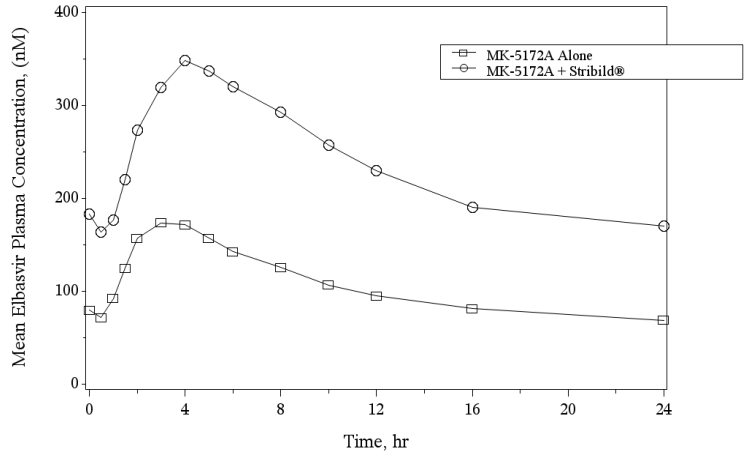
Grazoprevir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Zepatier™ Alone	
	GMR	90% CI
AUC_{0-24} ‡	5.36	(4.48, 6.43)
C_{max} ‡	4.59	(3.70, 5.69)
C_{24} ‡	2.78	(2.48, 3.11)

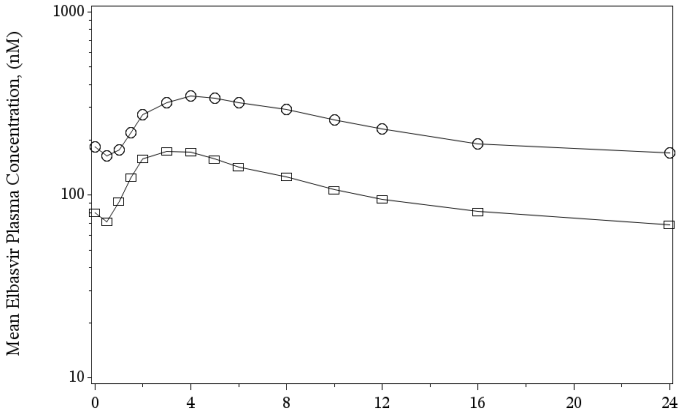
‡Back-transformed least-squares geometric mean ratio and confidence interval from linear mixed-effects model performed on natural log-transformed values.

- Zepatier™ and Stribild® co-administration increases steady state grazoprevir exposure via a combination of CYP3A and OATP1B1 inhibition

PK RESULTS: ELBASVIR

Grazoprevir (100 mg) | Elbasvir (50 mg)





Elbasvir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Zepatier™ Alone	
	GMR	90% CI
AUC_{0-24} ‡	2.18	(2.02, 2.35)
C_{max} ‡	1.91	(1.77, 2.05)
C_{24} ‡	2.38	(2.19, 2.60)

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

- Zepatier™ and Stribild® co-administration increases steady state elbasvir exposure via CYP3A inhibition

ZEPATIER™ AND STRIBILD DDI CONCLUSIONS

- Zepatier™ is generally safe and well-tolerated when co-administered with Stribild® in short term administration
- Co-administration of Zepatier™ and Stribild® has no meaningful effect on the steady state exposure of elvitegravir and emtricitabine
- Co-administration of Zepatier™ and Stribild® increases the steady state exposure of tenofovir (~1.2-fold, intestinal BCRP inhibition) and of cobicistat (~1.5-fold, CYP3A inhibition); these increases are not considered clinically meaningful
- Co-administration of Zepatier™ and Stribild® increases the steady state exposure of grazoprevir (~5.4-fold, combination of CYP3A and OATP1B1 inhibition) and of elbasvir (~2.2-fold, CYP3A inhibition)
- Due to the substantial increase in GZR exposure, co-administration of Zepatier™ with Stribild® is not recommended

ACKNOWLEDGEMENTS

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