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

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• Employee of Merck & Co.
BACKGROUND: ZEPATIER™

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

- HCV NS5A inhibitor
  - 50 mg once daily, oral

- Grazoprevir (MK-5172)

- Elbasvir (MK-8742)

- Broad activity against most HCV genotypes in vitro¹⁻²
- Efficacious in many sub-population of HCV patients: treatment-naïve & treatment-experienced, cirrhotic & non-cirrhotic, chronic kidney disease, HIV/HCV co-infected³⁻⁷
- Fixed-dose combination tablet once daily

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™
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
• 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 inhibition¹*
  – 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

- **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)

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-7</td>
<td>Days 1-10</td>
<td>Days 1-10</td>
</tr>
<tr>
<td><strong>Stribild</strong>® QD</td>
<td><strong>Zepatier</strong>™ QD</td>
<td><strong>Zepatier</strong>™ QD + <strong>Stribild</strong>® QD</td>
</tr>
<tr>
<td>5-Day Washout</td>
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</tbody>
</table>

- D7 PK (24 hr): EVG, FTC, TFV, COBI
- D10 PK (24 hr): GZR, EBR
- D10 PK (24 hr): EVG, FTC, TFV, COBI, GZR, EBR
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

Elvitegravir Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th></th>
<th>Zepatier™ + Stribild®/Stribild® Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMR</td>
<td>90% CI</td>
</tr>
<tr>
<td>AUC₀⁻₂₄ †</td>
<td>1.10</td>
</tr>
<tr>
<td>Cₘₐₓ †</td>
<td>1.02</td>
</tr>
<tr>
<td>Cₑ₂₄ †</td>
<td>1.31</td>
</tr>
</tbody>
</table>

†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

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

**Emtricitabine Pharmacokinetic Parameter**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zepatier™ + Stribild®/Stribild® Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMR</strong></td>
<td><strong>90% CI</strong></td>
</tr>
<tr>
<td>AUC(_{0-24}) ‡</td>
<td>1.07</td>
</tr>
<tr>
<td>C(_{\text{max}}) ‡</td>
<td>0.96</td>
</tr>
<tr>
<td>C(_{24}) ‡</td>
<td>1.19</td>
</tr>
</tbody>
</table>

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

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

### Tenofovir Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zepatier™ + Stribild® / Stribild® Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMR</strong></td>
<td><strong>90% CI</strong></td>
</tr>
<tr>
<td>AUC(_{0-24}) ‡</td>
<td>1.18 (1.13, 1.24)</td>
</tr>
<tr>
<td>C(_{\text{max}}) ‡</td>
<td>1.25 (1.14, 1.37)</td>
</tr>
<tr>
<td>C(_{24}) ‡</td>
<td>1.20 (1.15, 1.26)</td>
</tr>
</tbody>
</table>

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

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

### Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zepatier™ + Stribild® / Stribild® Alone</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; ‡</td>
<td>1.49</td>
<td>(1.42, 1.57)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; ‡</td>
<td>1.39</td>
<td>(1.29, 1.50)</td>
<td></td>
</tr>
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‡Back-transformed least-squares geometric mean ratio and confidence interval from linear mixed-effects model performed on natural log-transformed values.
PK RESULTS: GRAZOPREVIR

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

Grazoprevir Pharmacokinetic Parameter  |  Zepatier™ + Stribild®/Zepatier™ Alone
---|---
AUC₀-2₄ † | 5.36 (4.48, 6.43)
C_{max} † | 4.59 (3.70, 5.69)
C₂₄ † | 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.
PK RESULTS: ELBASVIR

Elbasvir Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zepatier™ + Stribild® / Zepatier™ Alone</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-2₄ ‡</td>
<td>2.18</td>
<td></td>
<td>(2.02, 2.35)</td>
</tr>
<tr>
<td>Cₘₐₓ ‡</td>
<td>1.91</td>
<td></td>
<td>(1.77, 2.05)</td>
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<tr>
<td>C₂₄ ‡</td>
<td>2.38</td>
<td></td>
<td>(2.19, 2.60)</td>
</tr>
</tbody>
</table>

‡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