DRUG-DRUG INTERACTIONS OF GLECAPREVIR AND PIBRENTASVIR WITH PRAVASTATIN, ROSUVASTATIN, OR DABIGATRAN ETEXILATE

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Direct-Acting Antiviral Agents (DAAs)

**Glecaprevir (GLE)**
- Pangenotypic NS3/4A protease inhibitor
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

**Pibrentasvir (PIB)**
- Pangenotypic NS5A inhibitor

**In vitro:**
- High barrier to resistance
- Retains activity against resistant associated HCV variants
- Additive/synergistic antiviral activity

**Clinical PK & metabolism:**
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

Glecaprevir and pibrentasvir are investigational new drugs. This material is not intended to suggest that any investigational drug discussed is safe or effective for the purposes for which it is under investigation.

GLE identified by AbbVie and Enanta.
Glecaprevir and Pibrentasvir as Transport Inhibitors

- Glecaprevir and pibrentasvir are potential inhibitors of multiple drug transporters including:
  - P-glycoprotein (P-gp)
  - Breast Cancer Resistance Protein (BCRP)
  - Organic Anion-Transporting Polypeptide (OATP) 1B1 and 1B3

- Coadministration with GLE + PIB increased exposure of P-gp and BCRP substrates
  - Digoxin (P-gp substrate): ↑ 72% $C_{\text{max}}$, ↑ 48% AUC
  - Sofosbuvir (P-gp and BCRP substrate): ↑ 66% $C_{\text{max}}$, ↑ 125% AUC
  - GS-331007 (Not a P-gp or BCRP substrate): ↔ $C_{\text{max}}$, ↔ AUC, ↑ 85% C$_{24}$

**Probe substrates of interest:**

<table>
<thead>
<tr>
<th>Pravastatin (OATP1B1/3 substrate)</th>
<th>• Less sensitive to transport inhibition than many other statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin (BCRP, OATP1B1/3 substrate)</td>
<td>• Larger potential increases due to involvement of multiple transporters</td>
</tr>
</tbody>
</table>
| Dabigatran Etexilate (P-gp substrate) | • Prodrug for dabigatran  
  • More sensitive to inhibition of intestinal P-gp than digoxin |

P-gp, BCRP, and OATP Expression

- P-gp and BCRP limit drug uptake (intestine) and promote efflux into bile (liver)
- OATP1B1 and OATP1B3 promote drug uptake into the liver
- Inhibition may increase systemic exposure of sensitive substrates
Pravastatin Study: Design

<table>
<thead>
<tr>
<th>Period 1 Day 1</th>
<th>8 Day Washout</th>
<th>Period 2 Days 1 to 3</th>
<th>Period 3 Days 1 to 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLE 400 mg QD + PIB 120 mg QD</td>
<td></td>
<td>Pravastatin 10 mg QD</td>
<td>GLE 400 mg QD + PIB 120 mg QD</td>
</tr>
</tbody>
</table>

- Phase 1 drug-drug interaction (DDI) study in N=12 healthy subjects
- All subjects provided written informed consent and study protocols were IRB approved
- Effect of multiple doses of GLE + PIB on multiple doses of pravastatin (Pravastatin exposure Period 3 Day 7 v. Period 2 Day 3)
- Effect of multiple doses of pravastatin on single dose of GLE + PIB (GLE and PIB exposures Period 3 Day 1 v. Period 1 Day 1)
Pravastatin Study: Results

Relative Bioavailability of Pravastatin, GLE and PIB

- When GLE + PIB and pravastatin were coadministered:
  - Pravastatin: ↑123% C_{max}, ↑130% AUC_{24}
  - GLE: ↑59% C_{max}, ↑44% AUC_{24}
  - No changes in PIB exposures (central value ratio 0.80 to 1.25)

- All enrolled subjects completed the study.
- All adverse events were mild in severity. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.
Pravastatin Study: Results (continued)

• Coadministration with drugs that increase systemic exposure of pravastatin may increase the risk of statin-associated myopathy, including rhabdomyolysis

• Increases in pravastatin exposure were similar to those observed with clarithromycin (↑ 127% $C_{\text{max}}$, ↑ 110% AUC)$^1$
  • When coadministered with clarithromycin, pravastatin dose should be limited to 40 mg per day (USPI) or used with caution (SmPC)

• Pravastatin dose should be reduced by 50% when used with GLE/PIB

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Rosuvastatin Study: Design

<table>
<thead>
<tr>
<th>Period 1 Day 1</th>
<th>Period 2 Days 1 to 7</th>
<th>Period 3 Days 1 to 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Day Washout</td>
<td>Rosuvastatin 5 mg QD</td>
<td>GLE 400 mg QD + PIB 120 mg QD</td>
</tr>
<tr>
<td>GLE 400 mg QD + PIB 120 mg QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Phase 1 drug-drug interaction (DDI) study in N=12 healthy subjects
- All subjects provided written informed consent and study protocols were IRB approved
- Effect of multiple doses of GLE + PIB on multiple doses of rosuvastatin (Rosuvastatin exposure on Period 3 Day 7 v. Period 2 Day 7)
- Effect of multiples doses of rosuvastatin on single dose of GLE + PIB (GLE and PIB exposures on Period 3 Day 1 v. Period 1 Day 1)
Rosuvastatin Study: Results

Relative Bioavailability of Rosuvastatin, GLE and PIB

- When GLE + PIB and rosuvastatin were coadministered:
  - Rosuvastatin: ↑ 462% C_{max}, ↑115% AUC_{24}
  - No changes in GLE or PIB exposures (central value ratio 0.80 to 1.25)

- One subject was discontinued from the rosuvastatin study arm after receiving a single dose of GLE + PIB alone due to the event of panic attack (Grade 2), which was assessed by the investigator as having no reasonable possibility of being related to study drug.
- The majority of adverse events were mild in severity. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.
Rosuvastatin Study: Results (continued)

- Coadministration with drugs that increase systemic exposure of rosuvastatin may increase the risk of statin-associated myopathy, including rhabdomyolysis

- Increases in rosuvastatin exposure were similar to those observed with lopinavir/ritonavir (↑ 366% $C_{\text{max}}$, ↑ 108% AUC)¹
  - When coadministered with lopinavir/ritonavir, rosuvastatin dose should be limited to 10 mg per day (USPI)

- Rosuvastatin dose should be limited to 10 mg per day when used with GLE/PIB

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# Dabigatran Etexilate Study: Design

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Days 2 to 3</th>
<th>Days 4 to 10</th>
<th>Day 11</th>
<th>Days 12 to 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate 150 mg single dose</td>
<td></td>
<td></td>
<td>Dabigatran etexilate 150 mg single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GLE 300 mg QD + PIB 120 mg QD</td>
<td></td>
</tr>
</tbody>
</table>

- Phase 1 drug-drug interaction (DDI) study in N=12 healthy subjects
- All subjects provided written informed consent and study protocols were IRB approved
- Effect of multiple doses of GLE + PIB on single dose dabigatran etexilate (Dabigatran exposure on Day 11 v Day 1)
- Effect of single dose dabigatran etexilate on multiple doses of GLE + PIB (GLE and PIB exposures on Day 11 v. Day 10)
Dabigatran Etexilate Study: Results

When GLE + PIB and dabigatran etexilate were coadministered:
- Dabigatran: ↑ 105% $C_{\text{max}}$, ↑ 138% $AUC_{\text{inf}}$
- No changes in GLE or PIB exposures (central value ratio 0.80 to 1.25)

One subject discontinued from the dabigatran study arm due to chemical exposure (Grade 1) assessed by the investigator as having no reasonable possibility of being related to study drug.

All other adverse events were mild in severity. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.
Dabigatran Etexilate Study: Results (continued)

- Increases in dabigatran exposure were similar to those observed with ketoconazole (↑ 135% to 149% AUC)\(^1\)

  - USPI dosing recommendations for dabigatran etexilate with ketoconazole:
    - CrCl > 50 mL/min: No dose adjustment
    - CrCl 30-50 mL/min: Reduce dabigatran etexilate dose to 75 mg BID
    - CrCl < 30 mL/min: Avoid Use

  - SmPC contraindicates use of ketoconazole and other “strong P-gp inhibitors” with dabigatran etexilate

- Dabigatran etexilate should be dosed per region specific labeling on use with P-gp inhibitors.

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Conclusions

- GLE and PIB are clinically relevant inhibitors of P-gp, BCRP, and OATP1B1/3.

- Coadministration with GLE + PIB increased systemic exposures of orally administered pravastatin, rosuvastatin, or dabigatran etexilate.

- Pravastatin and rosuvastatin may be used with GLE/PIB at a reduced or limited dose.

- Dabigatran etexilate should be dosed per region specific labeling on use with P-gp inhibitors when used with GLE/PIB.