Effect of Daclatasvir/Asunaprevir/Beclabuvir in Fixed-dose Combination on the Pharmacokinetics of CYP450/Transporter Substrates In Healthy Subjects

Xiaolu Tao¹, Karen Sims¹, Yi-Ting Chang¹, Jignasa Rana¹, Elsa Myers¹, Megan Wind-Rotolo¹, Rahul Bhatnagar², Timothy Eley¹, Tushar Garimella¹, Frank LaCreta¹, Malaz AbuTarif¹

¹Bristol-Myers Squibb Research and Development, Princeton, NJ, USA; ²PPD, Austin, TX, USA

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Presenting author: Tushar Garimella
Disclosures

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All-Oral DCV-TRIO Regimen

- **Daclatasvir (DCV)**
  - Pangenotypic NS5A inhibitor with low DDI potential
  - Substrate of CYP3A4 and P-gp
  - Inhibitor of P-gp, OATP1B1/B3 and BCRP; inducer of CYP3A4 (weak)

- **Asunaprevir (ASV)**
  - NS3 inhibitor
  - Substrate of CYP3A4, P-gp, OATP1B1/2B1
  - Inhibitor of CYP2D6, P-gp, OATP1B1/B3; inducer of CYP3A4

- **Beclabuvir (BCV) and BMS-794712 (BCV major metabolite)**
  - Nonnucleoside NS5B inhibitor
  - Substrates of CYP3A4 and P-gp (BCV)
  - Inhibitors of P-gp, OATP1B1/B3, BCRP, NTCP, BSEP; inducer of CYP3A4

- **DCV-TRIO**
  - DCV 30 mg / ASV 200 mg / BCV 75 mg in fixed-dose combination administered twice-daily
  - High rates of sustained virologic response and generally well-tolerated in Phase 3 studies\(^1,2\)

**Study AI443021 Objective**

- Assess the effect of steady-state DCV-TRIO on the PK of single-dose standard probe substrates for CYP enzymes and major human drug transporters (P-gp and OATP)

<table>
<thead>
<tr>
<th>CYP isozyme / transporter</th>
<th>Substrate</th>
<th>Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Caffeine</td>
<td>200</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Metoprolol</td>
<td>50</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Montelukast</td>
<td>10</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Flurbiprofen</td>
<td>50</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole</td>
<td>40</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>5</td>
</tr>
<tr>
<td>P-gp</td>
<td>Digoxin</td>
<td>0.25</td>
</tr>
<tr>
<td>OATP</td>
<td>Pravastatin</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) Administered as a validated cocktail with no internal DDIs
Study AI443021 Design

- **Patients**: Healthy subjects aged 18–45 years; BMI 18–32 kg/m²

- **PK blood sampling**:
  - DCV-TRIO: Pre-dose to 12 hours post-dose on Days 16 and 31
  - Probe / metabolite: Pre-dose to 120 hrs post-dose on Days 1, 16, 31

- **Analyses**: Point estimates of adjusted geometric mean ratios (GMR) and 90% confidence intervals (CIs) of $C_{\text{max}} / \text{AUC}_{\text{inf}}$ derived from a linear mixed-effect model

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Additional BCV added to account for higher BCV exposures in HCV patients relative to healthy subjects
Baseline and Demographic Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) years</td>
<td>31 (18–43)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Height, median (range) cm</td>
<td>177 (148–191)</td>
</tr>
<tr>
<td>Weight, median (range) kg</td>
<td>82 (59–108)</td>
</tr>
<tr>
<td>BMI, median (range) kg/m²</td>
<td>27 (19–31)</td>
</tr>
</tbody>
</table>

- 19/20 subjects (95%) completed the study
PK of DCV-TRIO Components

DCV and ASV exposures were comparable when administered as DCV-TRIO BID and DCV-TRIO + BCV 75 mg BID (during co-administration with cocktail).

DCV and ASV exposures during co-administration with cocktail were comparable with historic controls where DCV and ASV were administered alone or in combination\(^1\)

PK of DCV-TRIO Components

- Dose-proportional increases in BCV and BMS-794712 exposures were observed with additional BCV 75 mg BID (during co-administration with cocktail).
- BCV exposure following DCV-TRIO + BCV 75 mg BID was comparable with exposures observed in Phase 3 studies of DCV-TRIO (data on file).
Effect of DCV-TRIO on CYP1A2, CYP2C8 and CYP2C9

- DCV-TRIO BID had no clinically-meaningful effect on CYP1A2, CYP2C8 or CYP2C9
  - GMRs and 90% CIs of probe substrates were contained within the range of bioequivalence (0.80–1.25)
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)
Effect of DCV-TRIO on CYP2C19

DCV-TRIO BID caused weak-to-moderate induction of CYP2C19

- Omeprazole $C_{\text{max}}$ and $AUC_{0-T}$ decreased by 43% and 52%, respectively, during co-administration

DCV-TRIO + BCV 75 mg BID caused moderate induction of CYP2C19

- Omeprazole $C_{\text{max}}$ and $AUC_{0-T}$ decreased by 40% and 66%, respectively

CYP2C19 poor metabolisers (n=2) were excluded from the analyses

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

**Effect of DCV-TRIO on CYP2D6**

- **DCV-TRIO BID** caused weak-to-moderate inhibition of CYP2D6
  - Metoprolol $C_{\text{max}}$ and $\text{AUC}_{\text{inf}}$ increased by 40% and 71%, respectively during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)

- Impact of DCV-TRIO BID on the PK of metoprolol was less than the effect of ASV 200 mg BID alone at steady-state on the PK of single-dose dextromethorphan (CYP2D6 substrate)

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No CYP2D6 poor metabolisers were included in the current analyses;
Shaded area represents the accepted range of bioequivalence (0.8–1.25)

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Effect of DCV-TRIO on CYP3A4

DCV-TRIO caused weak to moderate induction of CYP3A4

- Midazolam $C_{\text{max}}$ and $AUC_{\text{inf}}$ decreased by 43% and 47%, respectively, during co-administration
- Additional BCV 75 mg BID had no further meaningful effect (data not shown)
- No additional impact from DCV / ASV was observed
- Degree of impact was comparable to the effect of steady-state BCV 150 mg alone (Study AI443-006)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

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1 AbuTarif M et al. 15th Int. Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, 2014: Poster PP_22.
DCV-TRIO BID caused weak inhibition of P-gp

- Digoxin $C_{\text{max}}$ and $\text{AUC}_{\text{inf}}$ both increased by 23% during co-administration
- Additional BCV 75 mg BID had no further meaningful effect (data not shown)
- Degree of impact on P-gp was comparable to that of DCV + ASV alone (Study AI447-040)\(^1\)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

\(^1\) Garimella T et al. Infectious Disease Week, 2014: Poster 822.
**Effect of DCV-TRIO on OATP**

- **DCV-TRIO BID inhibited OATP**
  - Pravastatin $C_{\text{max}}$ and $AUC_{\text{inf}}$ increased by 101% and 68%, respectively during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (AUC increased by a further 13%)
  - Effect of DCV-TRIO was comparable to that of DCV or ASV administered alone (using rosuvastatin as OATP probe)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

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Safety

- There were no deaths or serious adverse events
- One subject discontinued due to an AE (hemorrhoidal hemorrhage related to flurbiprofen)
- The most frequent AEs were constipation, nausea, and dizziness (all reported by three subjects each)
- All AEs were mild or moderate in intensity and resolved during the study
- No clinically significant changes in urinalysis, blood chemistry, electrocardiogram readings or vital signs were observed
Summary

- **DCV-TRIO has no effect on CYP1A2, 2C8, or 2C9**
- **DCV-TRIO is a moderate inducer of CYP2C19**
  - Induction of CYP2C19 was BCV dose-dependent
- **DCV-TRIO is a weak-to-moderate inhibitor of CYP2D6**
  - Impact of DCV-TRIO on exposure of metoprolol was less than the effect of ASV alone on the exposure of dextromethorphan
- **DCV-TRIO is a weak-to-moderate inducer of CYP3A4**
  - Comparable levels of induction were observed with BCV 150 mg alone, indicating no additive or synergistic effect on CYP3A4 induction when DCV, ASV and BCV are co-administered
- **DCV-TRIO is a weak inhibitor of P-gp**
  - P-gp inhibition by DCV-TRIO was comparable to that of DCV + ASV alone and indicates no additive / synergistic inhibition with the addition of BCV
- **DCV-TRIO is a weak-to-moderate inhibitor of OATP**
  - Inhibition of OATP was slightly higher with DCV-TRIO
Conclusions

- No dose adjustments are required during co-administration of DCV-TRIO FDC with substrates of CYP1A2, CYP2C9, CYP2C8, or P-gp
- Co-administration of DCV-TRIO FDC with substrates of CYP3A4, CYP2D6 or OATP should be approached with caution
- Co-administration of DCV-TRIO with drugs solely eliminated by CYP2C19 is not recommended