HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with Rifabutin, with or without Ritonavir, in Healthy Subjects

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BACKGROUND

- BMS-663068 is a prodrug metabolized to the active moiety BMS-626529, a first-in-class attachment inhibitor
- BMS-626529 is metabolized in part by CYP3A4, thus the potential for drug–drug interactions exists if PK measures:

RESULTS

Effect of rifabutin on the PK of BMS-626529

- **Cohort A:**
  - No change in the $\text{C}_{\text{max}}$ of BMS-626529 with coadministration of rifabutin compared to BMS-663068 alone
  - AUC$_{\text{tau}}$ (Day 15) of BMS-626529 increased by 30% with coadministration of rifabutin
  - The geometric mean ratio (GMR) of PK parameters of BMS-626529 with/without coadmedicated drug was ($0.98, 1.81$) for AUC$_{\text{tau}}$
  - No dose adjustment

Safety

- **Primary safety information in Table 3:**
- **Adverse events experienced by ≥5 subjects in Regimen C:**
  - Headache, nausea, diarrhea
  - No dose adjustment

Eye abnormalities

- **Regimen C:**
  - Eye abnormalities are part of the safety profile of rifabutin.

OBJECTIVES

- Primary outcome: assess the safety and tolerability of BMS-663068 administered alone, in combination with rifabutin, and in combination with rifabutin + ritonavir.

METHODS

A438401: Key inclusion criteria

- Healthy male and female subjects.
- 18–50 years of age.
- ART-naive, HIV-1-infected, treatment-experienced subjects.
- On regimen containing RTV, drug–drug interactions between rifabutin and BMS-663068 ± RTV might be expected.
- Six-week washout period from any antiretroviral therapy.
- A linear mixed-effect model with treatment as fixed effect and subject as repeated measures was fitted to PK parameters of BMS-626529 with/without coadministered drug.

A438401 study design

- A1438401 study design shown in Figure 2.
- A larger population size of 46 subjects was planned to ensure that at least 16 subjects per cohort would complete the study.

Figure 2: A438401 study design

Assessments

- **PK measures:**
  - Oral BMS-663068 serial blood samples were collected at 1, 2, 3, 6, 9, and 12 hours after dosing on Days 4 and 15.
  - Multiple PK parameters were obtained for each subject, including area under the concentration-time curve (AUC) from 0 to 12 hours (AUC$_{\text{0–12}}$). The PK parameters were analyzed using a linear mixed-effects model.

Statistical analysis

- A linear mixed-effect model with treatment as fixed effect and subject as random effect was fitted to the bivariate PK parameters (C$_{\text{max}}$, AUC$_{\text{0–12}}$) to calculate geometric mean ratios and 90% CI confidence intervals.

Table 1: PK results and statistical analysis: Effect of rifabutin on the PK of BMS-626529 (Cohort 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Cohort 1 (Regimen B)</th>
<th>Cohort 2 (Regimen C)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{\text{0–12}}$ (h*ng/mL)</td>
<td>BMS-663068</td>
<td>9,248 (7,160, 13,084)</td>
<td>10,304 (8,307, 13,271)</td>
<td>0.0463</td>
</tr>
<tr>
<td>AUC$_{\text{tau}}$ (h*ng/mL)</td>
<td>BMS-663068</td>
<td>13,111 (10,241, 16,707)</td>
<td>15,172 (12,298, 19,073)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Figure 3: Mean (±SD) PK profiles for BMS-626529

CONCLUSIONS

- **Dose modification is not required when coadministering BMS-663068 600 mg BID with rifabutin ± ritonavir:**
  - The observed AEs were consistent with the known safety profiles of rifabutin and ritonavir.
  - No new safety signals were identified for BMS-663068.
  - Changes in systemic exposure of BMS-663068, when given with rifabutin ± ritonavir, were not considered to be clinically meaningful.

Table 2: Interaction of BMS-663068 with other antiretroviral agents

<table>
<thead>
<tr>
<th>Drug (inf)</th>
<th>Drug (inf)</th>
<th>Cmax, AUC$<em>{\text{0–12}}$, or AUC$</em>{\text{tau}}$</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-663068</td>
<td>Ritonavir</td>
<td>5,160 (3,206, 8,275)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMS-663068</td>
<td>Ritonavir + RTV</td>
<td>5,315 (3,802, 7,453)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3: Safety summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>$n$</th>
<th>CV (%)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>BMS-663068</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NAs</td>
<td>BMS-663068</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Discontinuations</td>
<td>BMS-663068</td>
<td>1</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Summary of AEs experienced by ≥5 subjects

<table>
<thead>
<tr>
<th>AE</th>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3 (13.6)</td>
<td>4 (17.4)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4.3)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Chromaturia</td>
<td>1 (4.3)</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>0</td>
<td>0</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 5: Summary of laboratory abnormalities

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>4 (17.4)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (17.4)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ACKNOWLEDGMENTS

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REFERENCES