**BACKGROUND**

BMS-6630 is a prodrug of BMS-626529, a HIV-1 integrase inhibitor. Antiviral response during BMS-6630 monotherapy is assessed in Phase IIb trials. Dose-finding studies (AI438011) developed a population pharmacokinetic (PPK) model using BMS-663068 (68%) and BMS-626529 (32%) as active ingredients. A Phase IIb study (AI438006) used BMS-663068 (68%) and BMS-626529 (32%) as active ingredients. This study aimed to determine appropriate dose for the Phase III trials.

**OBJECTIVES**

- Determine a population pharmacokinetic (PPK) and exposure–response (ER) model.
- Use model-based simulation to project antiviral response as a function of BMS-626529 systemic exposure, and help select a Phase III dose.

**RESULTS**

### Subject demographics, demographics and disease characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51</td>
<td>18–75</td>
</tr>
<tr>
<td>Gender, n (%): Female</td>
<td>57 (32)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA copies/mL at baseline</td>
<td>78 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Median baseline CD4+ T-cell count, % (range)</td>
<td>28.6 (61)</td>
<td></td>
</tr>
<tr>
<td>Median baseline weight, kg (range)</td>
<td>74.9 (56–192)</td>
<td></td>
</tr>
<tr>
<td>Median baseline LBM, kg (range)</td>
<td>57 (32–83)</td>
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</tbody>
</table>

### Population PPK model

#### Pharmacokinetic (PK) description

- BMS-663068 and BMS-626529 are rapidly absorbed due to their efficient membrane permeability.
- BMS-663068 and BMS-626529 are both extensively metabolized in the liver by CYP3A4 and CYP3A5 enzymes.
- BMS-663068 and BMS-626529 are substrates of the P-glycoprotein transporter, leading to reduced systemic exposure when co-administered with P-glycoprotein inhibitors.

#### Population PK model

- The final model used described the relationship between log-transformed BMS-663068 systemic exposure and clinical pharmacodynamic parameters.
- Parameters were estimated using the maximum likelihood estimation method.

#### Exposure–response analysis

- A 95% confidence interval (CI) for the mean concentration–response relationship was derived from the final population PK model.
- The relationship between BMS-663068 systemic exposure and clinical pharmacodynamic parameters was assessed using the nonlinear mixed-effects model (NLME) framework.

#### Model-free simulations

- Simulation of the dose–response relationship for BMS-663068 was used to estimate the probability of achieving a >1 log decline in HIV-1 RNA.

**CONCLUSIONS**

- The final model provides a robust and statistically validated dose–response relationship for BMS-663068.
- The model was used to simulate the probability of achieving a >1 log decline in HIV-1 RNA for different dose regimens.
- The probability of achieving a >1 log decline in HIV-1 RNA was highest for BMS-663068 doses ranging from 400 mg BID to 1200 mg Q12H (with food).

**ACKNOWLEDGMENTS**

- The authors thank all trial participants and the trial teams for their contributions.
- The authors also thank the study sponsors and data management companies for their support.

**REFERENCES**

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