Exposure-Response Analyses of an Oral HIV Attachment Inhibitor BMS-663068 Following 8 Days of Monotherapy in HIV-Infected Patients

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12\textsuperscript{th} International Workshop on Clinical Pharmacotherapy of HIV Therapy
April 13-15, 2011; Miami, FL
Abstract O_08
Background

• BMS-663068 is the phosphate pro-drug of BMS-626529, a potent HIV-1 attachment inhibitor

• Generally well tolerated when dosed with an ER formulation with pharmacokinetic properties supportive of once or twice daily dosing
  – Nettles RE et al. HIV Clin Pharm Workshop. 2011; Abstract #O-04

• Achieved ‘proof-of-confidence” in HIV-1 infected subjects
  – Nettles RE et al. CROI. 2011; Abstract 49

• This work explored the exposure – response relationship for BMS-663068 based on POC monotherapy data
Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, Fl, USA

Proof of Concept Study: Design

HIV-1 clade B-infected males and females

Antiretroviral naive or experienced (off-treatment for > 8 weeks)

Plasma HIV-1 RNA > 5000 copies/mL

CD4+ T-cell Count > 200 cells/µL

Day 1

Day 8

Day 15

Day 50 (± 3 days)

Intense PK collection on Day 1 and Day 8

Outpatient visit

Outpatient visit and discharge

Treatment period

HIV ATTACHMENT INHIBITOR

BMS-663068 600 mg Q12H + RTV 100 mg Q12H N = 10

BMS-663068 1200 mg QHS + RTV 100 mg QHS N = 10

BMS-663068 1200 mg Q12H + RTV 100 mg Q12H N = 10

BMS-663068 1200 mg Q12H + RTV 100 mg QAM N = 10

BMS-663068 1200 mg Q12H N = 10

RTV: ritonavir

Nettles RE, et al. CROI, Feb 27-Mar 2, 2011; Boston, MA. Oral 49

Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, Fl, USA
Median Maximum Change in HIV-1 RNA From Baseline With Monotherapy

-1.64  -1.59  -1.78  -1.63  -1.22  -2.5  -2.0  -1.5  -1.0  -0.5  0

600 mg Q12H + 100 mg RTV Q12H (N = 9)
1200 mg QH + 100 mg RTV QHS (N = 9)
1200 mg Q12H + 100 mg RTV Q12H (N = 10)
1200 mg Q12h + 100 mg RTV QAM (N = 10)
1200 mg Q12H (N = 10)
Overall (N = 48)
Mean BMS-626529 Plasma Concentrations on Day 8

- Median protein binding adjusted IC₉₀ = 11.6 ng/mL (N = 46)

* Protein binding adjusted IC₉₀ (ng/mL) = sc × mw × IC₅₀ (μM)/fu; where sc is a factor that scales IC₉₀ from IC₅₀ (sc = 5.5); mw is the molecular weight of BMS-626529 free base (mw = 473.48 g/mole); fu is the mean estimated unbound faction of BMS-626529 (fu = 0.12)

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Nettles RE, et al. CROI, Feb 27-Mar 2, 2011; Boston, MA. Oral 49 HIV ATTACHMENT INHIBITOR

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BMS-626529 PK Exposures on Day 8

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$</th>
<th>$C_{\text{ssav}}$</th>
<th>$C_{\text{min}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 mg Q12H + RTV 100 mg Q12H (N = 10)</td>
<td>1.45 (1.16, 1.81)</td>
<td>1.42 (1.16, 1.74)</td>
<td>1.48 (0.97, 2.26)</td>
</tr>
<tr>
<td>1200 mg Q12H + RTV 100 mg QAM (N = 10)</td>
<td>1.51 (1.14, 1.98)</td>
<td>1.30 (0.99, 1.69)</td>
<td>1.17 (0.75, 1.83)</td>
</tr>
</tbody>
</table>

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No Apparent Relationship Between BMS-626529 Exposures and Maximum Change from Baseline in \log_{10} HIV-1 RNA
Baseline IC$_{50}$ vs Maximum Change from Baseline in Log$_{10}$ HIV-1 RNA

7 subjects had IC$_{50}$ values greater than the upper limit of the assay (0.1 µM)
Baseline IC$_{50}$: A Predictor of HIV-1 RNA Response

Model structure: Max RNA Change

\[ E_{max} \cdot IC_{50}^h / (EC_{50}^h + IC_{50}^h) \]

- $E_{max} = 1.88, EC_{50} = 0.2, h = -0.36$

IC$_{50}$ values re-assayed with extended upper limit of assay (10µM)

Solid line = fitted value; dashed line = 95% confidence intervals

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$C_{\text{min}}$ and $C_{\text{ssav}}$ Normalized to Baseline Susceptibility are Correlated with HIV-1 RNA Response

Solid line = fitted value; dashed line = 95% confidence intervals

$E_{\text{max}} = 1.87$
$EC_{50} = 0.08$
$h = 0.4$

$E_{\text{max}} = 1.85$
$EC_{50} = 0.34$
$h = 0.4$

Maximum change in log$_{10}$ HIV-1 RNA

600 mg Q12H + RTV 100 mg Q12H
1200 mg Q12H + RTV 100 mg Q12H
1200 mg Q12H + RTV 100 mg QAM
1200 mg Q12H

HIV ATTACHMENT INHIBITOR
Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, FL, USA
Distribution of Baseline Susceptibility Relative to BMS-626529 PK Exposures
High and Variable Baseline IC$_{50}$ Explains Lower HIV RNA Response in BMS-663068 1200 mg Q12H Arm
Population Distribution of Baseline IC$_{50}$

Sample source: POC (48), CASTLE (202), Other clinical samples (53)

IC$_{50}$ determined using Monogram Phenosense® Entry Assay; Upper limit of quantification 0.1 µM

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BMS-626529 Exposure vs Baseline Susceptibility
Lower Doses Than Studied May Suffice for Sensitive Virus
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Conclusions

- Baseline susceptibility (IC$_{50}$) is the most influential factor in determining the magnitude of decline in HIV-1 RNA

- Both $C_{\text{min}}$ and $C_{\text{ssav}}$ normalized to baseline susceptibility are correlated with antiviral activity
  - PK exposures alone are not predictive

- E-R analyses support further development of BMS-663068 in a virologically sensitive population at lower doses, given once or twice daily, without the requirement for RTV coadministration
  - A Phase IIb study in treatment-experienced subjects is planned to start in 2011