Atazanavir
(ATV, BMS-232632)

May 13, 2003
Introduction

Elliott Sigal, M.D., Ph.D.

Senior Vice President
Global Clinical and Pharmaceutical Development
Bristol-Myers Squibb
Atazanavir: Profile of a Novel Protease Inhibitor

- Meets evolving medical need
  - Distinct resistance profile
  - Favorable cholesterol and triglyceride profile
  - Decreased pill burden – Two pills once daily

- Acceptable safety/tolerability profile with well-characterized and manageable risks

- Demonstrates antiviral efficacy
Atazanavir Development Program

- Substantial clinical program demonstrating efficacy and safety
  - ~ 1000 antiviral treatment-naïve subjects studied on ATV with over 500 subjects treated for over 2 years
  - ~ 500 antiviral treatment-experienced subjects studied on ATV
  - Pediatric program ongoing

- Nine Phase II / III studies conducted

- Early Access Program with ~3600 patients enrolled to date

- Extensive characterization of safety profile
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard T. D’Aquila, M.D.</td>
<td>Director, Division of Infectious Diseases, Department of Medicine, The Addision B. Scoville Professor of Medicine, and Professor of Microbiology and Immunology, Vanderbilt University School of Medicine</td>
</tr>
<tr>
<td>Carl Grunfeld, M.D., Ph.D.</td>
<td>Professor of Medicine, University of California, San Francisco Metabolism and Endocrine Sections, Veterans Affairs Medical Center, San Francisco</td>
</tr>
<tr>
<td>Thomas Pearson, M.D., Ph.D.</td>
<td>Albert D. Kaiser Professor and Chair, Department of Community and Preventive Medicine and Senior Associate Dean for Clinical Research, University of Rochester School of Medicine</td>
</tr>
<tr>
<td>Craig Pratt, M.D.</td>
<td>Professor of Medicine and Director, Clinical Cardiology Research, Baylor College of Medicine Director Coronary Intensive Care Unit and Director, Non-Invasive Laboratories, The Methodist Hospital</td>
</tr>
<tr>
<td>Mark Ratain, M.D.</td>
<td>Leon O. Jacobson Professor of Medicine, Chairman, Committee on Clinical Pharmacology and Pharmacogenomics, and Associate Director for Clinical Science, Cancer Research Center, The University of Chicago</td>
</tr>
<tr>
<td>Name</td>
<td>Position</td>
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<tr>
<td>Jeremy Ruskin, M.D.</td>
<td>Associate Professor of Medicine, Harvard University Medical School</td>
</tr>
<tr>
<td></td>
<td>Director, Cardiac Arrhythmia Service, Massachusetts General Hospital</td>
</tr>
<tr>
<td>Richard Rutstein, M.D.</td>
<td>Associate Professor of Pediatrics, The University of Pennsylvania School of Medicine</td>
</tr>
<tr>
<td></td>
<td>Medical Director, Special Immunology Service, Children’s Hospital of Philadelphia</td>
</tr>
<tr>
<td>Kathleen Squires, M.D.</td>
<td>Associate Professor of Medicine, Keck School of Medicine, University of Southern California</td>
</tr>
<tr>
<td></td>
<td>Medical Director, Rand Schrader Clinic</td>
</tr>
<tr>
<td>Mark Sulkowski, M.D.</td>
<td>Assistant Professor of Medicine, Johns Hopkins University School of Medicine</td>
</tr>
<tr>
<td>Lee-Jen Wei, Ph.D.</td>
<td>Professor of Biostatistics, Harvard University</td>
</tr>
<tr>
<td>Allan W. Wolkoff, M.D.</td>
<td>Professor of Medicine and Anatomy &amp; Structural Biology and Director, Belfer Institute for Advanced Biomedical Studies, Albert Einstein College of Medicine</td>
</tr>
</tbody>
</table>
Atazanavir Proposed Indication

“Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.”
Bristol-Myers Squibb Presentation

- Steven M. Schnittman, M.D.
  - Clinical Development Program and Clinical Trial Results

- John H. Lawrence, M.D.
  - Cardiac Electrophysiology Evaluations

- Michael F. Giordano, M.D.
  - Characterization of Hyperbilirubinemia
  - Characterization of Lipid Profile

- Elliott Sigal, M.D., Ph.D.
  - Conclusion
Clinical Development Program and Clinical Trial Results

Steven M. Schnittman, M.D.

Vice President
Global Development
Bristol-Myers Squibb
Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients
ATV ADME Summary

Absorption
- Rapidly absorbed (Tmax ~ 1-3 hours)
- Food: ↑ exposure and ↓ intersubject variability
  - ATV to be administered with food

Distribution
- Protein Binding ~ 86% (albumin & \(\alpha_1\)-AG)

Metabolism
- Primarily metabolized by CYP3A4 like other PIs
- Inhibitor of CYP3A4 (Ki = 2.35 \(\mu\)M) like other PIs
  - NFV < ATV < LPV < RTV
- Inhibitor of UGT 1A1 (Ki = 1.9 \(\mu\)M, bilirubin glucuronidation)
  like indinavir

Elimination
- Primarily eliminated in feces
- Urinary excretion – 7% unchanged drug
- T\(\frac{1}{2}\) ~ 7 hours (supportive of once-daily dosing)
Drug Interactions Recommendations

No changes to either ATV or coadministered drug
- Atenolol
- Stavudine
- Lamivudine
- Zidovudine
- Ketoconazole

Modify dose and/or schedule of coadministered drug
- Saquinavir
- Clarithromycin
- Ethinyl estradiol / Norethindrone
- Rifabutin
- Diltiazem

Modify ATV dose or regimens
- Efavirenz
- Ritonavir

Separation in dosing from ATV
- Didanosine – buffered formulation
Rationale for ATV 400 mg Once Daily Treatment-Naïve Patients

Mean Plasma Concentration (SD) at Steady State (ng/mL)

Time (h)

PK Cushion

$C_{\text{max}}$

BMS-008 - ATV 400mg

$\text{In vitro Estimated Protein}$

Adjusted $EC_{90}$ Range 2.4 - 40.6 ng/mL

75th percentile

Median $\approx$ 14 ng/mL

25th percentile
## Rationale for ATV 400 mg Once Daily Treatment-Naïve Patients

<table>
<thead>
<tr>
<th></th>
<th>BMS-007</th>
<th>BMS-008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV 200</td>
<td>ATV 400</td>
</tr>
<tr>
<td>2-Week Mean RNA Decline (log₁₀ c/mL)</td>
<td>-1.18</td>
<td>-1.27</td>
</tr>
<tr>
<td>Hollow Fiber Model (RNA Suppression)</td>
<td>poor</td>
<td>good</td>
</tr>
<tr>
<td>Mean Cmin (ng/mL)</td>
<td>24*</td>
<td>150*</td>
</tr>
<tr>
<td>Grade 3 - 4 Total Bilirubin (&gt; 2.5 x ULN)</td>
<td>20%</td>
<td>41%</td>
</tr>
<tr>
<td>Grade 4 Total Bilirubin (&gt; 5 x ULN)</td>
<td>&lt; 1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Without regard to food
** With food

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**Core-14**
Summary of Efficacy in Phase II
Treatment-Naïve Subjects Through Week 48

<table>
<thead>
<tr>
<th></th>
<th>BMS-007</th>
<th>BMS-008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV 400 mg N = 78</td>
<td>ATV 400 mg N = 181</td>
</tr>
<tr>
<td></td>
<td>NFV N = 82</td>
<td>NFV N = 91</td>
</tr>
<tr>
<td>TLOVR (&lt; 400 c/mL)</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>68%</td>
<td>59%</td>
</tr>
<tr>
<td>Mean Change in HIV RNA (log$_{10}$ c/mL)</td>
<td>- 2.42</td>
<td>- 2.33</td>
</tr>
<tr>
<td></td>
<td>- 2.31</td>
<td>- 2.51</td>
</tr>
</tbody>
</table>
Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients
BMS-034 – Phase III Pivotal Study

Study Design

- Randomized, double-blind, double-dummy, active-controlled
- Treatment-naïve subjects: HIV RNA ≥ 2000 c/mL, CD4 ≥ 100 cells/mm³ (or > 75 cells/mm³ if no prior AIDS events)

1:1 Randomization, N = 810

- Treated N = 404
  - ATV 400 mg QD
  - EFV placebo QD
  - ZDV + 3TC BID (fixed dose)

- N = 401
  - EFV 600 mg QD
  - ATV placebo QD
  - ZDV + 3TC BID (fixed dose)
# BMS-034

## Subject Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment Regimen</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV / ZDV + 3TC N = 404</td>
<td>EFV / ZDV + 3TC N = 401</td>
<td></td>
</tr>
<tr>
<td>Median Age (Years)</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>38</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islanders</td>
<td>14</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Median HIV RNA Level (log_{10} c/mL)</td>
<td>4.87</td>
<td>4.91</td>
<td></td>
</tr>
<tr>
<td>HIV RNA Distribution (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30,000 c/mL</td>
<td>28</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>30,000 - &lt; 100,000 c/mL</td>
<td>30</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>≥ 100,000 c/mL</td>
<td>42</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Median CD4 Cell Count (cells/mm^3)</td>
<td>286</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>Hep B/C Co-Infected (%)</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
BMS-034

Virologic Response* Through Week 48
Intent to Treat (NC = F)

ATV-EFV Difference Estimate (95% CI): LOQ = 400 c/mL: 5.2 (-1.2, 11.7)
LOQ = 50 c/mL: -4.9 (-11.4, 1.5)

*TLOVR
**BMS-034**

**Virologic Response* Through Week 48 (ITT) by Baseline HIV RNA (LOQ = 400 c/mL)**

<table>
<thead>
<tr>
<th>Baseline HIV RNA (c/mL)</th>
<th>ATV</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100,000</td>
<td>74%</td>
<td>67%</td>
</tr>
<tr>
<td>≥ 100,000</td>
<td>64%</td>
<td>61%</td>
</tr>
</tbody>
</table>

*N = 235* 230 169 171

*TLOVR
### BMS-034

**I50L Identified in All ATV-Resistant Isolates**

<table>
<thead>
<tr>
<th></th>
<th>ATV N = 404</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virologic failure through 48 weeks</strong></td>
<td>69</td>
</tr>
<tr>
<td>Phenotypeable/Genotypeable, N</td>
<td>26</td>
</tr>
<tr>
<td>Phenotype &gt; 2.5 x IC$_{50}$ of control, N</td>
<td>6</td>
</tr>
<tr>
<td>I50L or I50I/L, N</td>
<td>6</td>
</tr>
</tbody>
</table>

Reasons for no result include: HIV RNA level ≤ 1000 c/mL (n = 44), isolate non-typeable (n = 23) or sample unavailable (n = 25)

*TLOVR (LOQ = 400 c/mL)*
Summary of ATV Resistance
Treatment-Naïve Subjects

- 23 on-study resistant isolates tested from Phase II and III studies
  - All have I50L signature mutation
  - I50L associated with
    - ATV-specific resistance
    - Decreased viral fitness
    - Phenotypic susceptibility maintained to other PIs
BMS-034

CD4 Cell Count Mean Increase From Baseline Treated Subjects

ATV-EFV TAD Estimate (95% CI) = 23.1 (9.7, 36.5)
## Grade 2 – 4 Related Adverse Events

<table>
<thead>
<tr>
<th>Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest</th>
<th>Subjects, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV N = 404</td>
</tr>
<tr>
<td>Total</td>
<td>165 (41)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Rash</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Scleral Icterus</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>
BMS-008: 467 Randomized in 2:2:1 ratio (Blinded to ATV Dose)

Group I
- 48 Wks
- Triple Therapy: ATV 400 mg QD d4T / 3TC

Group II
- 48 Wks
- Triple Therapy: ATV 600 mg QD d4T / 3TC

Group III
- 48 Wks
- Triple Therapy: NFV 1250 mg BID d4T / 3TC

BMS-044: 346 Treated

- ATV 400 mg QD d4T / 3TC
- ATV 600 mg QD d4T / 3TC
- Open-label ATV 400 mg QD d4T / 3TC
BMS-008/044
Virologic Response (AT)* Through Week 108 (LOQ = 400 c/mL)
Treated Subjects in BMS-044

*VR-OC (as treated)
BMS-008/044
CD4 Cell Count Mean Increase Through Week 108
Treated Subjects in BMS-044

CD4 Mean Change (SE) (cells/mm³)

Weeks

-50 0 50 100 150 200 250 300 350 400

B/L 12 24 36 48 60 72 84 96 108

ATV 400 (N = 139)
ATV 600 (N = 144)
NFV (N = 63)

NFV ⇒ ATV Transition

Treated Subjects in BMS-044

CD4 Cell Count Mean Increase Through Week 108

BMS-008/044

312
345
345

ATV Conclusions – Treatment-Naïve Subjects

- ATV 400 mg safe and effective
  - vs EFV in pivotal Phase III study
  - vs NFV in two Phase II studies
- Durable antiviral efficacy and safety
  - Dosing > 3 years
- Distinct resistance profile in treatment-naïve (I50L signature mutation)
- No increase in cholesterol, triglycerides
Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients
Treatment-experienced patients heterogeneous
- Prior ARV therapies and duration variable
- Generally ↓ phenotypic susceptibility, varied mutations

Several dosing strategies evaluated
- ATV 400 mg alone
- ATV boosted with ritonavir
- ATV combined with another PI (e.g., SQV)
Rationale for ATV 400 Unboosted Treatment-Experienced Patients

Selection of ATV 400 QD supported for Phase III study in subjects who failed a single PI (BMS-043)

- 551 clinical PI-resistant isolates: ATV susceptibility maintained vs 86% of isolates resistant to 1-2 approved PIs

- 400 mg QD dose provides mean Cmin ~150 ng/mL; Estimated median protein adjusted EC$_{90}$ 31.2 ng/mL (25 – 75 %-ile: 17.8 – 59.9 ng/ml)
BMS-043 - Phase III Pivotal Study

Study Design

Screening: Prior PI Failure

1:1 Randomization (N = 300)

Group I
- ATV 400 mg QD
- + 2 NRTIs

Treated 144
Efficacy Cohort* 114

Group II
- LPV / RTV 400/100 BID
- + 2 NRTIs

146
115

*Protocol-planned analysis which includes all subjects randomized through April 2, 2002 (≥ 24 weeks of therapy)
## BMS-043
### Subject Characteristics at Baseline Efficacy Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV N = 114</td>
</tr>
<tr>
<td>Median Age (Years)</td>
<td>36</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
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<tr>
<td>Hispanic/Latino</td>
<td>53</td>
</tr>
<tr>
<td>White</td>
<td>40</td>
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<tr>
<td>Black</td>
<td>6</td>
</tr>
<tr>
<td>Asian/Pacific Islanders</td>
<td>&lt;1</td>
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<tr>
<td>AIDS (%)</td>
<td>26</td>
</tr>
<tr>
<td>Median HIV RNA Level (log₁₀ c/mL)</td>
<td>4.19</td>
</tr>
<tr>
<td>Median CD4 Cell Count (cells/mm³)</td>
<td>279</td>
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<tr>
<td>Hep B/C Co-Infected (%)*</td>
<td>20</td>
</tr>
</tbody>
</table>

*All treated subjects*
Prior duration of antiretroviral drugs by class included:

- PIs 140 weeks
- NRTI 180 weeks
- NNRTI 85 weeks
# BMS-043

## PI Phenotypic Sensitivity at Baseline Efficacy Cohort

<table>
<thead>
<tr>
<th>PI</th>
<th>ATV N = 114</th>
<th>LPV / RTV N = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>APV</td>
<td>104 (91)</td>
<td>104 (90)</td>
</tr>
<tr>
<td>ATV</td>
<td>84 (74)</td>
<td>89 (77)</td>
</tr>
<tr>
<td>LPV</td>
<td>94 (82)</td>
<td>101 (88)</td>
</tr>
<tr>
<td>NFV</td>
<td>55 (48)</td>
<td>51 (44)</td>
</tr>
<tr>
<td>RTV</td>
<td>80 (70)</td>
<td>84 (73)</td>
</tr>
<tr>
<td>SQV</td>
<td>87 (76)</td>
<td>93 (81)</td>
</tr>
</tbody>
</table>

IC$_{50}$ ≤ 2.5 x CTL Subjects, N (%)
HIV RNA Mean Change – Co-Primary Endpoint 1

Efficacy Cohort

ATV - LPV/RTV TAD Estimate (97.5% CI) = 0.31 (0.06, 0.55)
ATV Contribution to Efficacy: Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV RNA log10 c/mL Change From Baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-043 ATP/NUC/NUC</td>
<td>-1.73</td>
</tr>
<tr>
<td>Overall dual NUC</td>
<td></td>
</tr>
<tr>
<td>Bartlett JA et al. ZDV/3TC (high dose)</td>
<td>-1.09 (-1.30, -0.88)</td>
</tr>
<tr>
<td>ZDV/3TC (low dose)</td>
<td></td>
</tr>
<tr>
<td>ZDV/ddC</td>
<td></td>
</tr>
<tr>
<td>Gulick RM et al. ZDV/3TC</td>
<td></td>
</tr>
<tr>
<td>Hammer SM et al. NUC/3TC</td>
<td></td>
</tr>
<tr>
<td>Hirsch M et al. ZDV/3TC</td>
<td></td>
</tr>
<tr>
<td>Raffi F et al. ddl/d4T</td>
<td></td>
</tr>
</tbody>
</table>

ATV/NUC/NUC - NUC/NUC Difference Estimate (95 CI) = -1.09 (-1.30, -0.88)
## BMS-043

### Virologic Response (ITT)* Through Week 24 Efficacy Cohort

<table>
<thead>
<tr>
<th>LOQ</th>
<th>ATV N = 114</th>
<th>LPV / RTV N = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOQ = 400 c/mL</td>
<td>61</td>
<td>81</td>
</tr>
<tr>
<td>LOQ = 50 c/mL</td>
<td>41</td>
<td>52</td>
</tr>
</tbody>
</table>

* TLOVR
<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>TLOVR (LOQ = 400 c/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI Phenotype $\leq 2.5 \times IC_{50}$ of control</td>
<td>68%</td>
</tr>
<tr>
<td>PI Phenotype $&gt; 2.5 \times IC_{50}$ of control</td>
<td>42%</td>
</tr>
<tr>
<td>One Prior PI</td>
<td>68%</td>
</tr>
<tr>
<td>$\geq 2$ Prior PIs</td>
<td>39%</td>
</tr>
<tr>
<td>No NRTI Mutations</td>
<td>59%</td>
</tr>
<tr>
<td>$\geq 1$ NRTI Mutation</td>
<td>61%</td>
</tr>
</tbody>
</table>
CD4 Cell Count Mean Increase From Baseline
Efficacy Cohort

ATV-LPV/RTV TAD Estimate (95% CI) = -25.3 (-49.8, -0.8)
Fasting LDL-Cholesterol Change From Baseline
Co-Primary Endpoint 2 – Efficacy Cohort

ATV - LPV/RTV Difference Estimate (97.5% CI) = -14.2 (-23.0, -5.4)
# BMS-043

## Grade 2 – 4 Related Adverse Events

<table>
<thead>
<tr>
<th>Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest</th>
<th>Subjects, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV N = 144</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV N = 144</td>
</tr>
<tr>
<td>26 (18)</td>
</tr>
</tbody>
</table>
Conclusions

- ATV 400 mg safe and effective
  - Majority of subjects achieve virologic response (< 400 c/mL)
  - Efficacy appears enhanced when subjects have ATV susceptibility $\leq 2.5 \times IC_{50}$ of control, exposure to only one prior PI, irrespective of NRTI mutations

- Superior lipid profile demonstrated

Efficacy with substantial lipid benefit
Dose-Selection Strategies
Highly Treatment-Experienced Patients

- Highly treatment-experienced patients
  - Extensive use of ARVs across all drug classes
  - Significant pheno- and genotypic resistance

- Two dosing strategies evaluated
  - ATV boosted with ritonavir
  - ATV combined with another PI, SQV
Rationale for ATV 300 Boosted with RTV 100
Treatment-Experienced Patients

Supports selection of ATV 300 / RTV QD dose for Phase III study in patients who failed multiple HAART regimens (BMS-045)
Subjects Who Failed ≥ 2 Regimens & ≥ 1 ARV from Each Class

1:1:1 Randomization (N = 358)

Wks 1–2: Maintain NRTIs & Replace PI / NNRTI

- ATV 300 mg QD
  - RTV 100 mg QD
- ATV 400 mg QD
  - SQV 1200 mg QD
- LPV 400 mg BID
  - RTV 100 mg BID

Wks 2 – 48: Replace NRTIs with tenofovir 300 mg QD + 1 NRTI

Randomized 120 115 123
BMS-045: Antiviral Efficacy

HIV RNA Mean Change From Baseline Through Week 24
Randomized Subjects

HIV RNA Mean Change (SE) (log_{10} c/mL)

- **ATV 300/RTV (N = 120)**
- **ATV 400/SQV (N = 115)**
- **LPV/RTV (N = 123)**

ATV 300/RTV – LPV/RTV TAD Estimate (97.5% CI) = 0.14 (-0.09, 0.37)
ATV 400/SQV – LPV/RTV TAD Estimate (97.5% CI) = 0.31 (0.07, 0.55)
# BMS-045

## Virologic Response (ITT)* Through Week 24

Randomized Subjects

* TLOVR

<table>
<thead>
<tr>
<th></th>
<th>% Undetectable</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV 300 / RTV</td>
<td>ATV 400 / SQV</td>
<td>LPV / RTV</td>
</tr>
<tr>
<td></td>
<td>N = 120</td>
<td>N = 115</td>
<td>N = 123</td>
</tr>
<tr>
<td>LOQ = 400 c/mL</td>
<td>64</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>LOQ = 50 c/mL</td>
<td>39</td>
<td>23</td>
<td>42</td>
</tr>
</tbody>
</table>

LOQ = 400 c/mL
LOQ = 50 c/mL
Virologic Response (ITT)* Through Week 24
Randomized Subjects – ATV/RTV vs LPV/RTV

For LOQ = 400 c/mL:
ATV 300/RTV – LPV/RTV Difference Estimate (95% CI) = 2.4 (-9.8, 14.5)
BMS-045
CD4 Cell Count Mean Increase From Baseline
Randomized Subjects

<table>
<thead>
<tr>
<th>Weeks</th>
<th>B/L</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **ATV 300/RTV (N = 120)**
- **ATV 400/SQV (N = 115)**
- **LPV/RTV (N = 123)**

**ATV 300/RTV – LPV/RTV TAD Estimate (95% CI) -18.4 (-44.3, 7.5)**

**ATV 400/SQV – LPV/RTV TAD Estimate (95% CI) -44.9 (-74.5, 15.3)**
## BMS-045
Grade 2 – 4 Related Adverse Events
Week 24

<table>
<thead>
<tr>
<th>Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest</th>
<th>Subjects, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATV 300 / RTV N = 119</td>
</tr>
<tr>
<td>Total</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
</tr>
<tr>
<td>Scleral Icterus</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>
Conclusions

- Safety and efficacy for ATV 300 / RTV 100 similar to LPV / RTV through 24 weeks (unreviewed)
Overall Clinical Conclusions of Efficacy and General Safety

- Durable efficacy in treatment-naïve patients vs EFV, NFV
- Efficacy of ATV 400 QD demonstrated in treatment-experienced patients
- Distinct resistance profile (I50L) in treatment-naïve and susceptible experienced patients
- Safe and well-tolerated at 400 QD
  - Hyperbilirubinemia / jaundice are dose-related and manageable
  - Consistent, durable lipid profile may provide reduced CV risk
- Drug-drug interactions well characterized
- Early data indicate safety and efficacy of ATV 300 QD boosted with RTV
Cardiac Electrophysiology Evaluations

John H. Lawrence, M.D.

Executive Director
Clinical Design and Evaluation
Bristol-Myers Squibb
Introduction
Electrophysiology Evaluations

- Preclinical assessments
  - \textit{In vitro} and \textit{in vivo} studies

- QTc and PR intervals and changes from baseline
  - 8 studies in healthy volunteers
    (N = 254 ATV; 28\% females)
  - 5 studies in HIV-infected subjects
    (N = 1037 ATV, 31\% females; N = 629 comparator, 28\% females)
Electrophysiologic Effects of ATV in Preclinical Studies

<table>
<thead>
<tr>
<th>Ion Channel Assay</th>
<th>Purkinje Fiber Action Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na Block</td>
<td>Ca Block</td>
</tr>
<tr>
<td>&gt; 30 μM (16% @ 30 μM)</td>
<td>10.4 μM</td>
</tr>
<tr>
<td>HERG Block</td>
<td>&gt; 30 μM (15% @ 30 μM)</td>
</tr>
<tr>
<td>↑ Duration (APD$_{90}$) at 30 μM</td>
<td>13%</td>
</tr>
</tbody>
</table>

- All PIs tested blocked HERG channels or prolonged action potential duration with *in vitro* potency similar to or greater than ATV
- No ECG changes in 9 month dog toxicology study
BMS-076
Study Design

- Double-blind, placebo-controlled, three-treatment crossover study

- Randomized treatment sequence (N = 72 subjects)
  - Placebo, 400 mg ATV, 800 mg ATV

- 6 day treatment period with ≥ 14 day washout period

- Serial ECGs and PK samples

- Primary endpoints:
  - QTc and PR intervals and changes from baseline on Day 6 of each treatment period
**QTc Introduction**

- **Heart rate correction of QT**
  - Bazett formula: \( QTc_B = \frac{QT}{RR^{1/2}} \)
  - Fridericia formula: \( QTc_F = \frac{QT}{RR^{1/3}} \)

- **Mean \( \Delta HR \) ↑ 3.5 beats/min at 400 mg ATV  
  ↑ 8.2 beats/min at 800 mg ATV**

- **QTc assessments**
  - Mean change from baseline
  - Individual subjects with prolonged QTc
  - Concentration-dependence of QTc changes
### BMS-076 QTc Data (using Bazett’s Formula)

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N = 67</td>
</tr>
<tr>
<td>ΔQTcB Avg (msec), Mean (SD)</td>
<td>-3 (10)</td>
</tr>
<tr>
<td>ΔQTcB Max (msec), Mean (SD)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>ΔQTcB Tmax (msec), Mean (SD)</td>
<td>-15 (20)</td>
</tr>
<tr>
<td>QTcB &gt; 500 msec, N</td>
<td>0</td>
</tr>
<tr>
<td>ΔQTcB &gt; 60 msec, N</td>
<td>1</td>
</tr>
</tbody>
</table>
## BMS-076 QTc Data (using Fridericia’s Formula)

### ECG Parameter

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo N = 67</th>
<th>ATV 400 N = 65</th>
<th>ATV 800 N = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔQTcF Avg (msec), Mean (SD)</td>
<td>-4 (8)</td>
<td>-6 (8)</td>
<td>-5 (11)</td>
</tr>
<tr>
<td>ΔQTcF Max (msec), Mean (SD)</td>
<td>11 (13)</td>
<td>6 (13)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>ΔQTcF Tmax (msec), Mean (SD)</td>
<td>-9 (17)</td>
<td>-15 (13)</td>
<td>-8 (17)</td>
</tr>
<tr>
<td>QTcF &gt; 500 msec, N</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ΔQTcF &gt; 60 msec, N</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Concentration vs QTcF

- **Concentration (ng/mL)**
  - 0 to 2000
  - 2000 to 4000
  - 4000 to 6000
  - 6000 to 8000
  - 8000 to 10000
  - 10000 to 12000
  - 12000 to 14000
  - 14000 to 16000
  - 16000 to 18000
  - 18000 to 20000

- **QTcF (msec)**
  - 300 to 320
  - 320 to 340
  - 340 to 360
  - 360 to 380
  - 380 to 400
  - 400 to 420
  - 420 to 440
  - 440 to 460
  - 460 to 480
  - 480 to 500

### Graphical Representation

- The scatter plot shows the relationship between concentration and QTcF.
- N values for each condition are indicated at the bottom of the table.
### Comparator Studies of QTc Data in HIV-infected Subjects

<table>
<thead>
<tr>
<th>QTcF (msec)</th>
<th>QTc Intervals&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ATV&lt;sup&gt;b&lt;/sup&gt; N = 864</th>
<th>Comparators&lt;sup&gt;c&lt;/sup&gt; N = 629</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>451 - 500</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>471 - 500</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes data from BMS-041, BMS-034, BMS-043, BMS-045  
<sup>b</sup>In study BMS-045, ATV is co-administered with either ritonavir or saquinavir  
<sup>c</sup>Comparators included nelfinavir, lopinavir/ritonavir, ritonavir, and efavirenz
Summary QTc Interval

QTc Interval

- No concentration-dependent effect of ATV on QTcF
- No QTcF > 500 msec or ΔQTcF > 60 msec
- QTc results comparable to comparator drugs
PR Introduction

- Clinical significance of AV block
  - 1° AVB (PR > 200 msec)
    - Asymptomatic, no change in heart rate
  - 2° AVB or 3° AVB
    - Symptoms related to ventricular rate

- PR assessments
  - Mean change from baseline
  - Individual subjects with prolonged PR
  - Dose-dependence of PR prolongation
## Maximum PR Interval Data

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N = 67</td>
</tr>
<tr>
<td>△ PR Max (msec), Mean (SD)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>1° AV Block, N (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>2° or 3° AV Block, N (%)</td>
<td>0</td>
</tr>
</tbody>
</table>
# PR Interval Prolongation Similar for ATV and Comparators

<table>
<thead>
<tr>
<th>PR Interval (msec)</th>
<th>Number with AV Block (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ATV&lt;sup&gt;b&lt;/sup&gt; N = 864</th>
<th>NFV&lt;sup&gt;c&lt;/sup&gt; N = 48</th>
<th>EFV&lt;sup&gt;d&lt;/sup&gt; N = 329</th>
<th>LPV / RTV&lt;sup&gt;e&lt;/sup&gt; N = 252</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° AV Block, N (%)</td>
<td>44 (5)</td>
<td>5 (10)</td>
<td>10 (3)</td>
<td>13 (5)</td>
<td></td>
</tr>
<tr>
<td>2° or 3° AV Block, N (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup>Includes data from BMS-041, BMS-034, BMS-043, BMS-045

<sup>b</sup>In study BMS-045, ATV is co-administered with either ritonavir or saquinavir

<sup>c</sup>Comparator for study BMS-041

<sup>d</sup>Comparator for study BMS-034

<sup>e</sup>Comparator for studies BMS-043 and BMS-045
Summary PR Interval

PR Interval

- Dose-related PR prolongation
- PR prolongation limited to 1st-degree AV block (with rare exceptions)
- Incidence of PR prolongations comparable between ATV and comparators
Conclusions
Cardiac Electrophysiology

- ATV has no effect on the QTc interval
- ATV has manageable effects on the PR interval that are comparable to several other HIV drugs
- As with other PIs, caution advised when ATV is co-administered with drugs known to prolong the QTc or PR intervals that are metabolized by CYP3A4
Characterization of Hyperbilirubinemia

Michael F. Giordano, M.D.
Group Director
Clinical Design and Evaluation
Bristol-Myers Squibb
Laboratory Bilirubin Elevations

Total bilirubin elevations identified early in ATV clinical development

- Principally unconjugated bilirubin
  - Using HPLC – entirely unconjugated

- ~ 50% Grade 1-2 (≤ 2.5 x ULN)

- ~ 25% Grade 3 (2.6 – 5 x ULN)

- ~ 5% Grade 4 (> 5 x ULN)

- Reversible within days
Atazanavir Bilirubin Elevations

- Review mechanisms of bilirubin production
  - UGT 1A1 enzyme inhibition as seen with PI indinavir
  - Related to benign inherited condition, Gilbert’s Syndrome

- Description of clinical manifestation
  - No relationship to hepatic toxicity
    - Includes large number of hepatitis co-infection
    - Clinical signs and symptoms infrequent

- Patient Management plan
Bilirubin Production and Metabolism

- #1 Hemolysis
- #2 Transport
- #3 Uptake
- #4 IC Transport*
- #5 Glucuronidation
- #6 Export

- B
- B*ALBUMIN
- GST + B
- UGT 1A1 enzyme
- B • G1 or • G2

* Intracellular transport
Common UGT 1A1 polymorphism is responsible for Gilbert’s Syndrome

ATV inhibition of UGT 1A1 – same mechanism as indinavir*

UGT 1A1 genotype predicts bilirubin level in patients on ATV

Total and Direct Bilirubin
ATV 400 mg Treatment-Naïve Subjects (N = 683)

Number with Measurements
Total: 683 650 628 615 572 471 376 217 194 182 167 76
Direct: 679 649 627 615 572 470 376 217 194 183 167 76

Studies BMS-034, BMS-007 and BMS-008
BMS-045
Total and Direct Bilirubin
ATV 300 / RTV 100 Subjects (N = 119)

Number with Measurements

<table>
<thead>
<tr>
<th></th>
<th>Total:</th>
<th>Direct:</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/L</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
<td>117</td>
</tr>
<tr>
<td>8</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>16</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>20</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>24</td>
<td>112</td>
<td>112</td>
</tr>
</tbody>
</table>

Weeks

Median Bilirubin (mg/dL)

- **Total**: Median bilirubin levels show a peak around week 8, followed by a gradual decrease.
- **Direct**: Median bilirubin levels remain relatively stable throughout the weeks.
Total Bilirubin Elevations and Clinical Events

- **Naïve subjects BMS-034**
  - 6% bilirubin > 5 x ULN
  - 11% jaundice
  - 11% scleral icterus
  - < 1% D/C due to hyperbilirubinemia

- **Experienced subjects ATV 300/RTV**
  - 9% bilirubin > 5 x ULN
  - 15% jaundice
  - 10% scleral icterus
  - 0 D/C due to hyperbilirubinemia
BMS-034
Treatment-Naïve Subjects
Transaminase and Bilirubin Elevations Not Associated
ATV + ZDV / 3TC

<table>
<thead>
<tr>
<th>ALT (SGPT)</th>
<th>Bilirubin Grade 0 - 2 (≤ 2.5 X ULN) N = 271</th>
<th>Bilirubin Grade 3 - 4 (&gt; 2.5 X ULN) N = 131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 - 2 (≤ 5 X ULN)</td>
<td>262 (96%)</td>
<td>125 (95%)</td>
</tr>
<tr>
<td>Grade 3 - 4 (&gt; 5 X ULN)</td>
<td>9 (4%)</td>
<td>6 (5%)</td>
</tr>
</tbody>
</table>

Median follow-up: 52 weeks
Grade 3 – 4 ALT Elevations
In Phase III ATV Studies

<table>
<thead>
<tr>
<th>ALT (SGPT)</th>
<th>Naïve Subjects</th>
<th>Experienced Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naïve Subjects</td>
<td>Experienced Subjects</td>
</tr>
<tr>
<td></td>
<td>BMS-034</td>
<td>BMS-043</td>
</tr>
<tr>
<td>ATV 400</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>EFV</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>ATV 400</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>LPV / RTV</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>N = 404</td>
<td></td>
<td>119</td>
</tr>
<tr>
<td>N = 144</td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>N = 401</td>
<td></td>
<td>119</td>
</tr>
<tr>
<td>LPV / RTV</td>
<td></td>
<td>118</td>
</tr>
<tr>
<td>N = 118</td>
<td></td>
<td>110</td>
</tr>
</tbody>
</table>

Median Time on Therapy: BMS-034 (52 weeks); BMS-043 (24 weeks); BMS-045 (24 weeks)
## Grade 3 – 4 ALT Elevations in Co-Infected Subjects

### ATV vs Comparators

#### Overall Frequency of ALT > 5 x ULN

<table>
<thead>
<tr>
<th></th>
<th>ATV</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hep B/C +</strong></td>
<td>13/131  (10)</td>
<td>10/88 (11)</td>
</tr>
<tr>
<td><strong>Hep B/C -</strong></td>
<td>20/777  (3)</td>
<td>8/542 (1)</td>
</tr>
</tbody>
</table>

BMS-008, BMS-034, and BMS-043
Unconjugated Hyperbilirubinemia

Conclusions

- Frequency and magnitude thoroughly described
  - Not associated with hepatotoxicity based on mechanism and clinical ALT data
  - Benign and manageable
  - Frequency of dose-limiting hyperbilirubinemia / jaundice not different from AE profile for other ARVs
  - No evidence for long-term sequelae
Hyperbilirubinemia Management

- Physician and Patient Education
  - What to expect
  - Extend upon the indinavir experience

- LFT monitoring above standard of care not anticipated

- Recommendation
  - Alternative therapy should be considered if patients experience total serum bilirubin concentrations $> 5 \times \text{ULN}$
Characterization of Lipid Profile
Introduction
Atazanavir Lipid and Metabolic Profile

- Lipid and metabolic problem with current PIs
- Lower cholesterol and triglycerides for ATV
  - Magnitude, durability assessed
  - Consistent data in treated and naïve subjects and ARV combinations
- Reduced need for lipid lowering therapy
- CV risk related to cholesterol and metabolic effects
  - Established for general population
  - Data in HIV and HAART evolving
  - NCEP recommended for HIV
Other PI Regimens Increase Cholesterol and Triglyceride

- APV: 35, 32
- NFV: 28, 30
- SQV: 34, 37
- RTV: 35
- IDV: 33
- LPV/RTV: 26, 26

% Change from Baseline

- Cholesterol
- Triglycerides

Naïve subjects receiving PI-based first-line regimen

All measurements following ≥ 4 weeks of treatment

BMS-034

No Effect on LDL-C for ATV: Treatment-Naïve Subjects

ATV (N = 404)

EFV (N = 401)

Difference Estimate (95% CI) = -14.1 (-18.0, -9.9)
BMS-034

No Effect on Triglycerides for ATV: Treatment-Naïve Subjects

Difference Estimate (95% CI) = -26.1 (-32.2, -19.4)
BMS-044

Durability of Lipid-Neutral Effects for ATV: LDL-Cholesterol Results Through 2 Years

![Graph showing the durability of lipid-neutral effects for ATV and NFV through 2 years. The graph plots mean LDL cholesterol levels (mg/dL) over weeks for ATV 400 (N = 139) and NFV (N = 63). The y-axis represents mean LDL (SE) in mg/dL, ranging from 90 to 135, and the x-axis represents weeks from B/L to 108.]
BMS-044

Improvement in Lipids After Switch to ATV: Mean Change From Entry to Week 24

Mean Change (mg/dL)

<table>
<thead>
<tr>
<th>Measure</th>
<th>ATV 400</th>
<th>NFV ⇒ ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-36</td>
<td>-37</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-27</td>
<td>-33</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Core-87
### Hyperlipidemia Management for HIV-Infected Individuals

Use NCEP (National Cholesterol Education Program) Adult Treatment Panel III Guidelines

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>LDL-Cholesterol (mg/dL)</th>
<th>Non-HDL-Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or risk equivalent</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>≥ 2 risk factors and 10-year risk ≤ 20%</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>0-1 risk factors</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
</tr>
</tbody>
</table>

Lipid Lowering Thresholds Based on NCEP Categories for ATV and Comparator – ARV Naïve

* BMS-034 (Week 48)
Lipid Lowering Thresholds Based on NCEP Categories for ATV and Comparator ARV Switch and Experienced Subjects

- **Baseline On-Rx**: 27%
- **On-Rx**: 10%

**NCEP Categories**
- **LDL-C ≥ 160 mg/dL**: 28%
- **LDL-C 130 - 159 mg/dL**: 10%
- **LDL-C 100 - 129 mg/dL**: 20%
- **LDL-C 70 - 99 mg/dL**: 17%
- **LDL-C < 70 mg/dL**: 6%

**Switches**
- NFV ⇒ ATV
- X ⇒ ATV
- X ⇒ LPV / RTV

**Comparators**
- BMS-043

* BMS-044 (Week 24), BMS-043 (Week 24)
Importance of ATV Metabolic Profile Summary

- Maintaining favorable metabolic profile in HIV is important and challenging

- Problems with other PIs and statins / lipid lowering drugs
  - Statins complicate already complex regimens
  - Introduce potential toxicity and intolerance
  - Introduce potential drug-drug interactions
  - NCEP treatment goals frequently not achieved
    - for triglycerides in particular
Importance of ATV Metabolic Profile Summary

- ATV results in little or no detrimental effects
  - Cholesterol and triglycerides
  - Durable (108 weeks) and consistent results
  - Naïve and experienced, gender, race
  - Variety of companion ARVs
  - Improved lipids achieved after switch to ATV

- Unique benefit of ATV
  - Avoid lipid lowering therapy
  - May avoid unnecessary additional CV risk factor
Conclusion

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Risk-Benefit Assessment: Risks

- Adverse events generally mild
- Hyperbilirubinemia
  - Mild, manageable, and reversible
- Cardiac electrophysiology changes minimal
  - PR prolongation manageable
Risk-Benefit Assessment: Benefits

- Demonstrated antiviral efficacy
- Durable treatment effect
- Favorable lipid profile
- Unique resistance profile
- Once daily 2-pill regimen