Clinical Development Program and Clinical Trial Efficacy Results

Howard Mayer, MD
Pfizer Global Research & Development

Overview

• Overview of the maraviroc Phase 2b/3 development program

• Clinical results in treatment-experienced patients with R5-tropic HIV-1

• Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1
Overview

- Overview of the maraviroc Phase 2b/3 development program
- Clinical results in treatment-experienced patients with R5-tropic HIV-1
- Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1

Maraviroc Phase 2b/3 Program

<table>
<thead>
<tr>
<th></th>
<th>ARV-naïve</th>
<th>ARV-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R5 Patients</td>
<td>R5 Patients</td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td>1026</td>
<td>1027</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td>2b→3</td>
<td>2b/3</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>MVC vs. EFV +CBV</td>
<td>OBT add-on</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td>1:1:1</td>
<td>2:2:1</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>%&lt;400/&lt;50 wk 48/96</td>
<td>Δ VL at wk 24/48</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>917</td>
<td>601</td>
</tr>
<tr>
<td><strong>Received maraviroc</strong></td>
<td>467</td>
<td>373</td>
</tr>
</tbody>
</table>

ARV – antiretroviral, EFV – efavirenz (Sustiva), VL – viral load
OBT – optimized background therapy, CBV – Combivir
**HIV-1 Tropism at Screening**

Maraviroc Phase 2b/3 Program

Coakley et al. 2nd Int Workshop Targeting HIV Entry, October 2006

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**Maraviroc Dosing Strategy**

300 mg Dose Equivalent – QD and BID

<table>
<thead>
<tr>
<th>Concomitant Antiretrovirals</th>
<th>Maraviroc Unit Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 PI (excluding tipranavir/ritonavir) and/or delavirdine (± efavirenz)</td>
<td>150 mg *</td>
</tr>
<tr>
<td>All other regimens (including tipranavir/ritonavir)</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

* Dose adjustment based on not significantly exceeding a 300 mg equivalent C\text{\text{max}}.

Overview

- Overview of the maraviroc Phase 2b/3 development program
- Clinical results in treatment-experienced patients with R5-tropic HIV-1
- Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1

Trial Design

**A4001027 and A4001028**

- Randomization 1:2:2
  - A4001027 N = 601
  - A4001028 N = 475

- **OBT* + placebo**
- **OBT* + maraviroc QD**
- **OBT* + maraviroc BID**

Patients were stratified by enfuvirtide use and HIV-1-RNA < and ≥ 100,000 c/mL

Patient eligibility criteria:
- R5 HIV-1 infection
- HIV-1-RNA ≥ 5,000 c/mL
- Stable pre-study ARV regimen, or no ARVs for ≥ 4 weeks
- Resistance to and/or ≥ 6 months experience with ≥ one ARV from three classes (≥ two for PIs)

* OBT = 3–6 ARVs
Primary and Secondary Endpoints
A4001027 and A4001028

• Primary Efficacy Endpoint
  ‣ Change from baseline in log\textsubscript{10} transformed HIV-1 RNA levels
  ‣ Discontinuation = no change from baseline

• Key Secondary Endpoints
  ‣ Percentage of subjects with HIV-1 RNA < 400 c/mL
  ‣ Percentage of subjects with HIV-1 RNA < 50 c/mL
  ‣ Change from baseline in CD4\(^+\) cell count*

* LOCF = Last Observation Carried Forward

A4001027: Results
US, Canada
## Demographics and Baseline Characteristics

Includes all patients who received at least one dose of study medication

<table>
<thead>
<tr>
<th></th>
<th>Placebo + OBT N=118</th>
<th>MVC QD + OBT N=232</th>
<th>MVC BID + OBT N=235</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, yrs (range)</strong></td>
<td>46 (31–71)</td>
<td>46 (19–75)</td>
<td>46 (25–69)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>106 (90)</td>
<td>210 (91)</td>
<td>212 (90)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>99 (84)</td>
<td>187 (81)</td>
<td>197 (84)</td>
</tr>
<tr>
<td><em><em>Median CD4 count</em>, cells/mm³ (range)</em>*</td>
<td>163 (1–675)</td>
<td>168 (1–812)</td>
<td>150 (2–678)</td>
</tr>
<tr>
<td><em><em>Mean HIV-1 RNA</em>, log₁₀ c/mL (range)</em>*</td>
<td>4.84 (3.46–6.02)</td>
<td>4.85 (3.20–6.75)</td>
<td>4.86 (3.26–6.88)</td>
</tr>
<tr>
<td><strong>Enfuvirtide in OBT, %</strong></td>
<td>42</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>≤ 2 active drugs in OBT (OSS), %</td>
<td>66</td>
<td>69</td>
<td>76</td>
</tr>
</tbody>
</table>

* Baseline for each patient calculated as the mean of up to three pre-dose assessments (screening, randomization, and baseline visit)

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## Mean Change in HIV-1 RNA from Baseline at Week 24

Includes all patients who received at least one dose of study medication

- **Placebo + OBT N = 118**: Mean Change = -1.03, 97.5% CI: -1.14, -0.94
- **MVC QD + OBT N = 232**: Mean Change = -1.82, 97.5% CI: -2.07, -1.57
- **MVC BID + OBT N = 235**: Mean Change = -1.95, 97.5% CI: -2.25, -1.65

Difference: -0.79 (97.5% CI: -1.14, -0.44)
Patients with Undetectable HIV-1 RNA at Week 24

Includes all patients who received at least one dose of study medication

- Placebo (N = 118)
- Maraviroc QD (N = 232)
- Maraviroc BID (N = 235)

< 400 copies/mL

- p < 0.0001
- p = 0.0001

< 50 copies/mL

- p < 0.0001
- p < 0.0006

Mean Change in CD4 Count from Baseline at Week 24

Includes all patients who received at least one dose of study medication (LOCF)

- Placebo + MVC QD + MVC BID

- p < 0.0001
  - Difference: +55 (95% CI: 30, 79)
  - Difference: +59 (95% CI: 35, 83)

Mean Change in CD4 Count (cells/mm³)

- 52
- 107
- 111

Placebo + OBT
MVC QD + OBT
MVC BID + OBT
N = 116
N = 227
N = 233
# A4001028: Results

Europe, Australia and US

## Demographics and Baseline Characteristics

Includes all patients who received at least one dose of study medication

<table>
<thead>
<tr>
<th>Randomized N = 475</th>
<th>Placebo + OBT N=91</th>
<th>MVC QD + OBT N=182</th>
<th>MVC BID + OBT N=191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (range)</td>
<td>45 (29–72)</td>
<td>45 (17–75)</td>
<td>47 (21–73)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>79 (87)</td>
<td>153 (84)</td>
<td>170 (89)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>79 (87)</td>
<td>149 (82)</td>
<td>166 (87)</td>
</tr>
<tr>
<td>Median CD4 count*, cells/mm³ (range)</td>
<td>174 (2–545)</td>
<td>174 (1–966)</td>
<td>182 (3–820)</td>
</tr>
<tr>
<td>Mean HIV-1 RNA*, log₁₀ c/mL (range)</td>
<td>4.89 (3.75–7.07)</td>
<td>4.87 (2.49–6.33)</td>
<td>4.84 (2.96–6.22)</td>
</tr>
<tr>
<td>Enfuvirtide in OBT, %</td>
<td>45</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>≤ 2 active drugs in OBT (OSS), %</td>
<td>66</td>
<td>63</td>
<td>62</td>
</tr>
</tbody>
</table>

* Baseline for each patient calculated as the mean of up to three pre-dose assessments. (screening, randomization, and baseline visit)
Mean Change in HIV-1 RNA from Baseline at Week 24

Includes all patients who received at least one dose of study medication

Placebo + OBT
N = 91

MVC QD + OBT
N = 182

MVC BID + OBT
N = 191

Difference: -1.02
(97.5% CI: -1.43, -0.62)

Difference: -1.04
(97.5% CI: -1.44, -0.64)

Patients with Undetectable HIV-1 RNA at Week 24

Includes all patients who received at least one dose of study medication

Placebo (N = 91)

Maraviroc QD (N = 182)

Maraviroc BID (N = 191)

< 400 copies/mL

< 50 copies/mL
Mean Change in CD4 Count from Baseline at Week 24

Includes all patients who received at least one dose of study medication (LOCF)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean Change in CD4 Count (cells/mm³)</th>
<th>p Value</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + OBT</td>
<td>90</td>
<td>64</td>
<td>&lt; 0.001</td>
<td>+48 (22, 74)</td>
</tr>
<tr>
<td>MVC QD + OBT</td>
<td>180</td>
<td>112</td>
<td>&lt; 0.001</td>
<td>+38 (12, 64)</td>
</tr>
<tr>
<td>MVC BID + OBT</td>
<td>185</td>
<td>102</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combined A4001027 and A4001028 Co-administered ARVs
Patients with HIV-1 RNA < 50 c/mL by Protease Inhibitor use in OBT (Week 24)

Includes all patients who received at least one dose of study medication

- Placebo
- Maraviroc QD
- Maraviroc BID

Patients with HIV-1 RNA < 50 c/mL by Enfuvirtide use in OBT (Week 24)

Includes all patients who received at least one dose of study medication

- Placebo
- Maraviroc QD
- Maraviroc BID
Patients with HIV-1 RNA < 50 c/mL by Enfuvirtide/LPV-RTV First use in OBT (Week 24)

Includes all patients who received at least one dose of study medication

- Placebo
- Maraviroc QD
- Maraviroc BID

Patients with HIV-1 RNA < 400 c/mL by Enfuvirtide/LPV-RTV First use in OBT (Week 24)

Includes all patients who received at least one dose of study medication
Combined A4001027 and A4001028 Maraviroc QD vs BID

Patients with HIV-1 RNA < 50 c/mL by Screening HIV-1 RNA (Week 24)

Includes all patients who received at least one dose of study medication

<table>
<thead>
<tr>
<th>HIV-1 RNA (copies/mL)</th>
<th>Placebo</th>
<th>Maraviroc QD</th>
<th>Maraviroc BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100,000</td>
<td>34</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>≥100,000</td>
<td>11</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Total Population</td>
<td>25</td>
<td>48</td>
<td>48</td>
</tr>
</tbody>
</table>

N = 123 238 243 84 419
Patients with HIV-1 RNA < 50 c/mL by Baseline CD4 Count (Week 24)

Includes all patients who received at least one dose of study medication

Patients with HIV-1 RNA < 50 c/mL by Number of Active Drugs (Week 24)

Includes all patients who received at least one dose of study medication
Pharmacokinetic/Pharmacodynamic Analysis
Maraviroc QD vs BID

All ARV Experienced – 150 mg QD Group
Single PI vs. Phase 2a 300 mg BID

LPV= Lopinavir
ATV= Atazanavir
r = ritonavir
FPV= Fosamprenavir
SQV= Saquinavir
IDV= Indinavir
All ARV Experienced – 150 mg BID Group
Single PI vs. Phase 2a 300 mg BID

LPV= Lopinavir
ATV= Atazanavir
r = ritonavir
FPV= Fosamprenavir
SQV= Saquinavir
IDV= Indinavir

All ARV Experienced – 300 mg QD and BID
in the Presence and Absence of Tipranavir/ritonavir

TPV= Tipranavir
r = ritonavir
Exposure Response Efficacy Analysis
A4001027 and A4001028

- Endpoints
  - Virology
    - VL < 50 copies/mL at week 24
    - VL < 400 copies/mL at week 24
    - Failure at week 4: VL > 400 copies/mL or decrease from baseline less than -1 log_{10} copies/mL
  - CD4+ cell count change from baseline at week 24

- Method: Generalized additive modeling (GAM)

- Prognostic factors tested included:
  - Dose + compliance or C_{min}, or C_{av}
  - Baseline viral load, CD4, tropism phenotype
  - Number of active drugs, PI use, ENF use, etc
  - Demographics

Probability of Failure (HIV-1 RNA > 50 c/mL)
As a Function of the MVC C_{min} and C_{av} (Week 24)
Combined A4001027 and A4001028: Tropism Change

Mean Change in CD4 Count from Baseline by Tropism Results in Treatment Failures

<table>
<thead>
<tr>
<th>Tropism Result, Baseline → Treatment Failure</th>
<th>Placebo + OBT N=209</th>
<th>MVC QD + OBT N=414</th>
<th>MVC BID + OBT N=426</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatment failures</td>
<td>+14 (n=97)</td>
<td>+49 (n=68)</td>
<td>+71 (n=77)</td>
</tr>
<tr>
<td>R5 → R5</td>
<td>+15 (n=80)</td>
<td>+61 (n=18)</td>
<td>+138 (n=17)</td>
</tr>
<tr>
<td>R5 → D/M or X4</td>
<td>+67 (n=4)</td>
<td>+37 (n=31)</td>
<td>+56 (n=32)</td>
</tr>
<tr>
<td>Non-R5 → Any</td>
<td>+15 (n=8)</td>
<td>+54 (n=11)</td>
<td>+26 (n=19)</td>
</tr>
</tbody>
</table>
Patients with HIV-1 RNA < 50 c/mL by Tropism at Baseline (Week 24)

Includes all patients who received at least one dose of study medication

Dual/Mixed CCR5 Total Population

Maraviroc QD
Maraviroc BID
Placebo

Percent of Patients

N= 17 33 33 18 7 362 377 207 408 419

Tropism Results on Follow-up in Patients Failing with D/M or X4-tropic HIV-1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>D/M or X4-tropic virus at last follow-up</th>
<th>R5-tropic virus at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Patients</td>
<td>Median Days</td>
<td># of Patients</td>
</tr>
<tr>
<td>MVC All</td>
<td>44</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>MVC QD</td>
<td>23</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>MVC BiD</td>
<td>21</td>
<td>5</td>
<td>121</td>
</tr>
<tr>
<td>Placebo</td>
<td>3</td>
<td>2</td>
<td>22</td>
</tr>
</tbody>
</table>
Overview

- Overview of the maraviroc Phase 2b/3 development program
- Clinical results in treatment-experienced patients with R5-tropic HIV-1
- Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1

Demographics and Baseline Characteristics

Includes all patients who received at least one dose of study medication

<table>
<thead>
<tr>
<th></th>
<th>Placebo + OBT N=62</th>
<th>MVC QD + OBT N=63</th>
<th>MVC BID + OBT N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (range)</td>
<td>45 (23–65)</td>
<td>43 (16–59)</td>
<td>43 (16–62)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>53 (86)</td>
<td>53 (84)</td>
<td>55 (90)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>40 (65)</td>
<td>46 (73)</td>
<td>44 (72)</td>
</tr>
<tr>
<td>Median CD4 count, cells/mm³ (range)</td>
<td>42¹ (2, 650)</td>
<td>40² (1, 442)</td>
<td>43* (0, 615)</td>
</tr>
<tr>
<td>Mean HIV-1 RNA, log₁₀ c/mL (range)</td>
<td>5.01¹ (3.65, 6.15)</td>
<td>5.03² (3.43, 5.94)</td>
<td>5.10* (3.61, 6.67)</td>
</tr>
<tr>
<td>Enfuvirtide in OBT, %</td>
<td>56</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>D/M at Screening, n</td>
<td>58</td>
<td>57</td>
<td>52</td>
</tr>
</tbody>
</table>

¹N=58, ²N=57, *N=52, **N=54
Mean Change in HIV-1 RNA from Baseline at Week 24

Includes all patients with D/M-tropic HIV-1 who received at least one dose of study medication

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change from Baseline (log10 copies/mL)</th>
<th>Difference</th>
<th>97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + OBT</td>
<td>-0.97</td>
<td>+0.06</td>
<td>(-0.53, +0.64)</td>
</tr>
<tr>
<td>MVC QD + OBT</td>
<td>-0.91</td>
<td>-0.23</td>
<td>(-0.83, +0.36)</td>
</tr>
<tr>
<td>MVC BID + OBT</td>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with Undetectable HIV-1 RNA at Week 24

Includes all patients with D/M-tropic HIV-1 who received at least one dose of study medication

<table>
<thead>
<tr>
<th>Group</th>
<th>&lt; 400 copies/mL</th>
<th>p-value</th>
<th>&lt; 50 copies/mL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 58)</td>
<td>26.9</td>
<td>0.15</td>
<td>15.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Maraviroc QD (N = 57)</td>
<td>30.8</td>
<td>0.93</td>
<td>24.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Maraviroc BID (N = 52)</td>
<td>30.8</td>
<td>0.45</td>
<td>24.6</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Mean Change in CD4 Cell Count from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo + OBT</th>
<th>MVC QD + OBT</th>
<th>MVC BID + OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated patients with D/M-tropic HIV-1</td>
<td>+36 (n=58)</td>
<td>+60 (n=57)</td>
<td>+62 (n=52)</td>
</tr>
<tr>
<td>Difference MVC – Placebo (95% CI)</td>
<td>N/A</td>
<td>+24 (-1.36, 49.21)</td>
<td>+26 (0.87, 52.49)</td>
</tr>
<tr>
<td>Patients discontinuing due to treatment failure</td>
<td>+4 (n=23)</td>
<td>+38 (n=33)</td>
<td>+25 (n=21)</td>
</tr>
<tr>
<td>Patients with only X4-tropic HIV-1 detectable at time of treatment failure</td>
<td>-104 (n=2)</td>
<td>+48 (n=12)</td>
<td>+33 (n=12)</td>
</tr>
</tbody>
</table>

* Data for 4 patients is missing, D/M - dual/mixed-tropic, LOCF.

Mayer H et al. 16th IAC 2006; abstract THLB0215

Summary

• In treatment-experienced patients with R5-tropic HIV-1 and few remaining treatment options, maraviroc + OBT demonstrated significantly greater virologic suppression and CD4 cell increases compared with placebo + OBT.

• There are subgroups of patients where there appears to be an efficacy difference between maraviroc BID and maraviroc QD:
  - HIV-1 RNA ≥ 100,000 c/mL
  - Very low CD4
  - No other active ARVs
Summary

• Patients with R5-tropic HIV-1 failing on maraviroc had mean increases in CD4 count that were greater than placebo even when failing in the context of a change in tropism

• Of patients with R5-tropic virus at baseline who failed on maraviroc + OBT, nearly twice as many patients had a change in tropism to D/M-tropic or X4-tropic as compared with remaining R5-tropic
  ‣ The virus in most patients who failed on maraviroc with D/M-tropic or X4-tropic virus reverted back to R5-tropic during the follow-up period

Summary

• In treatment-experienced patients with D/M-tropic HIV-1, maraviroc + OBT did not lead to a significantly greater reduction in HIV-1 RNA, but was also not associated with an adverse virologic outcome and demonstrated greater CD4 increases as compared with placebo + OBT
  ‣ These results were also observed in those patients (7.6%) in studies 1027 and 1028, who had a change in tropism from R5-tropic to D/M-tropic between screening and baseline
Agenda and Speakers

- Introductions, Background and Overview of Maraviroc
  Michael Dunne MD, Therapeutic Area Head, Development, Infectious Diseases

- Clinical Efficacy
  Howard Mayer MD, Global Clinical Leader, Pfizer

- Safety and Tolerance
  Steve Felstead MB ChB, Maraviroc Team Leader, Pfizer

- In Vitro and In Vivo Tropism and Resistance Evaluation
  Mike Westby PhD, Virology Team Leader, Pfizer

- Medical Need and Place in HIV Armamentarium
  Dan Kuritzkes MD, Brigham and Women’s Hospital, Harvard Medical School, Boston

- Conclusions
  Michael Dunne MD

Safety and Tolerance of Maraviroc

Steve Felstead, MB ChB
Pfizer Global Research & Development