Maraviroc in Treatment Experienced Patients Infected with CCR5 - Tropic HIV-1

FDA Advisory Committee
Silver Spring, MD
24th April 2007

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
**Proposed Indication**

Maraviroc, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1

**Maraviroc**

This data review has some important characteristics:

- The chemotype is from a novel chemical class
- The antiviral target is a human receptor
- The receptor engages immune mediators
- Successful inhibition of the underlying HIV infection will also effect the immune system
- Inherent tropism of the virus potentially selects for a second pathway of resistance, with virus that may behave differently

The most integrated basis upon which to generate a risk / benefit assessment will be derived from human data collected from trials in the target population
Chemokine Receptors and HIV Cell Entry

HIV-1 Entry Cofactor: Functional cDNA Cloning of a Seven-Transmembrane, G Protein-Coupled Receptor


Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene


Discovery of CCR5 and Impact on HIV Pathogenesis
Patients Heterozygous for CCR5 Δ32 Have Slower Progression to AIDS and Death

After Attachment to CD4 - Fusion Occurs When the V3 Loop Binds to Either CCR5 or CXCR4


Adapted from Moore JP et al. PNAS 2003;100:10598-10602.
Molecular Model of CCR5, gp120 and Maraviroc Binding Sites

Trofile™ HIV Entry Cell Assay

Antagonists are used to confirm results
**Trofile™ HIV Entry Cell Assay**

- **Transfection**
  - HIV genomic luc vector
  - HIV env expression vector

- **Infection**
  - R5 HIV only
  - Dual-Mixed HIV-1

- **Antagonists are used to confirm results**


Terms Used to Define Tropism

<table>
<thead>
<tr>
<th>Tropism</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5-tropic</td>
<td>Only CCR5-tropic virus detected in the assay</td>
</tr>
<tr>
<td>X4-tropic</td>
<td>Only CXCR4-tropic virus detected in the assay</td>
</tr>
<tr>
<td>D/M (dual/mixed) tropic</td>
<td>Both CCR5-tropic and/or CXCR4-tropic and/or Dual Tropic virus detected in the assay</td>
</tr>
</tbody>
</table>

Percentage of HIV Co-receptor Usage

<table>
<thead>
<tr>
<th>Study/Source</th>
<th>Population</th>
<th>N</th>
<th>R5</th>
<th>X4</th>
<th>R5/X4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homer cohort1</td>
<td>Naïve</td>
<td>979</td>
<td>82%</td>
<td>&lt;1%</td>
<td>18%</td>
</tr>
<tr>
<td>C &amp; W cohort2</td>
<td>Naïve</td>
<td>402</td>
<td>81%</td>
<td>&lt;1%</td>
<td>19%</td>
</tr>
<tr>
<td>Demarest3</td>
<td>Naïve</td>
<td>299</td>
<td>88%</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>TORO 1/24</td>
<td>Experienced</td>
<td>612</td>
<td>50%</td>
<td>4%</td>
<td>46%</td>
</tr>
<tr>
<td>Monogram5</td>
<td>Experienced</td>
<td>&gt;2000</td>
<td>48%</td>
<td>2%</td>
<td>50%</td>
</tr>
<tr>
<td>ACTG 52116</td>
<td>Experienced</td>
<td>391</td>
<td>49%</td>
<td>4%</td>
<td>47%</td>
</tr>
</tbody>
</table>

* This table may not include all available reported data. Majority of data are generated in the developed world (subtype B)

Maraviroc Overview

Pre-clinical Profile

- Selective, functional, reversible CCR5 antagonist
  - Antagonises binding of endogenous CCR5 ligands
- Active \textit{in vitro} versus R5-tropic HIV-1
  - Inactive versus X4-tropic or R5X4-tropic HIV-1
  - Serial passage found R5 resistant isolates emerging slowly
- Cross-clade potency against primary CCR5-tropic isolates
- Mean IC$_{90} = 2.0$ nM

Absorption and Distribution

- Absorption is non-linear at doses <100 mg
  - Increasingly linear thereafter
- Distribution is widespread
  - High concentrations in lymph nodes
  - CSF concentration is 10% of plasma (rat)

Metabolism and Excretion

- Maraviroc is extensively metabolised via CYP3A4
  - No effect on other cytochrome p450 enzyme pathways
  - No CYP3A4 induction/inhibition
  - No effect of maraviroc on other drugs
    - midazolam, β-OH-cortisol/cortisol
- Maraviroc is a p-glycoprotein substrate
- Excretion is primarily fecal
  - 23% of drug related material excreted in the urine
- Metabolites have no activity/affinity at/for any receptor at relevant concentrations
**Human Pharmacokinetics**

- Rapid absorption with $T_{\text{max}}$ 0.5 - 4.0 hours
- Modelled terminal $T_{1/2}$ of 17 hours
- PK similar across gender, race, patients/volunteers
- Limited accumulation on multiple dosing (<20%)
- High fat meal reduces exposure with blunting of $C_{\text{max}}$ (↓33%)
  - $C_{\text{min}}$ and AUC correlate best with efficacy

**Drug-Drug Interaction Program**

**Effect of ‘other drugs’ on maraviroc**
- Ketoconazole
- Saquinavir (± rtv)
- Lopinavir/ritonavir
- Ritonavir
- Atazanavir (± rtv)
- Darunavir/ritonavir
- Efavirenz
- Rifampicin
- Lopinavir/ritonavir + efavirenz
- Saquinavir/ritonavir + efavirenz
- Tipranavir/ritonavir
- HAART (SD probe study)
  - Efavirenz + lamivudine/zidovudine (Combivir)
  - Lopinavir/ritonavir + lamivudine + stavudine
  - Efavirenz + didanosine EC + tenofovir N
  - Nevirapine + lamivudine + tenofovir
- Sulfamethoxazole/trimethoprim
- Tenofovir

**Effect of maraviroc on ‘other drugs’**
- Oral Contraceptives
  - Ethinylestradiol
  - Levnorgestrel
- Midazolam
- Debrisoquine metabolic ratio
- 6beta-hydroxycortisol/cortisol ratio
- Zidovudine/lamivudine (Combivir)
CYP3A4 Drugs Can Affect Metabolism

- CYP3A4 inhibitors increase maraviroc exposure
  - Ketoconazole, protease inhibitors, delavirdine
    - AUC (↑3-10x) and C\text{max} (↑2-5x)
  - But no change with tipranavir/ritonavir

- CYP3A4 inducers decrease maraviroc exposure
  - AUC and C\text{max} decreased by 50-70%
    - Efavirenz, rifampin

- Combinations of inhibitors/inducers lead to inhibition
  - Saquinavir/ritonavir + efavirenz; Kaletra® + efavirenz

- Renal substrates/inhibitors do not affect maraviroc PK
  - Co-trimoxazole, tenofovir

Rationale for Dose Selection
Phase 2a Monotherapy

Study population: asymptomatic, CD4 >250, RS-tropic (N=82); BL VL ~42K

Rationale for Dose Selection and Adjustment

- Maraviroc was very well tolerated to 300 mg BID
  - Postural hypotension observed at 600 mg, related to C\text{max}
- 300 mg QD and BID at plateau of antiviral effect
- Drugs which affect CYP3A4 can influence maraviroc concentrations
  - Dose adjustment to 150 mg for CYP3A4 inhibitors is, overall, most clinically appropriate
    - Corrects for C\text{max}, under corrects for AUC
  - Dose adjustment to 600 mg for CYP3A4 inducers corrects for both C\text{max} and AUC

Phase 2b/3 Program

<table>
<thead>
<tr>
<th>ARV-naïve</th>
<th>ARV-experienced</th>
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<tbody>
<tr>
<td>R5 Patients</td>
<td>R5 Patients</td>
</tr>
<tr>
<td>Study</td>
<td>1026</td>
</tr>
<tr>
<td>Phase</td>
<td>2b→3</td>
</tr>
<tr>
<td>Design</td>
<td>MVC vs. EFV + CBV</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1:1</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>%&lt;400/&lt;50 wk 48/96</td>
</tr>
<tr>
<td>Enrollment</td>
<td>917</td>
</tr>
<tr>
<td>Received Maraviroc</td>
<td>467</td>
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</tbody>
</table>

ARV = antiretroviral, EFV = efavirenz (Sustiva), VL = viral load
OBT = optimized background therapy, CBV = Combivir
Phase 2b/3 Program

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<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Enrollment</th>
<th>Enrollment</th>
<th>Enrollment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>124</td>
<td>373</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>2b</td>
<td>2b/3</td>
<td>2b/3</td>
<td>2b</td>
</tr>
<tr>
<td>Design</td>
<td>MVC vs. EFV+CBV</td>
<td>OBT add-on</td>
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<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1:1</td>
<td>2:2:1</td>
<td>2:2:1</td>
<td>1:1:1</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>%&lt;400/&lt;50 wk 48/96</td>
<td>Δ VL at wk 24/48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received Maraviroc</td>
<td>467</td>
<td>373</td>
<td>124</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Patient Exposure

<table>
<thead>
<tr>
<th></th>
<th>Maraviroc</th>
<th>Comparator</th>
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</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>299</td>
<td>-</td>
</tr>
<tr>
<td>Multiple dose</td>
<td>333</td>
<td>-</td>
</tr>
<tr>
<td>Phase 2a</td>
<td>66</td>
<td>16</td>
</tr>
<tr>
<td>Total Short Term Studies</td>
<td>698</td>
<td>16</td>
</tr>
<tr>
<td>Phase 2b/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Experienced R5 patients (1027 &amp; 1028)</td>
<td>840</td>
<td>209</td>
</tr>
<tr>
<td>Treatment Experienced nonR5 patients (1029)</td>
<td>124</td>
<td>62</td>
</tr>
<tr>
<td>Total Treatment Experienced patients</td>
<td>964</td>
<td>271</td>
</tr>
<tr>
<td>Open Label from placebo (1027 &amp; 1028)</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Naïve, QD regimen (1026)</td>
<td>174</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>1910</td>
<td>287</td>
</tr>
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ARV - antiretroviral, EFV - efavirenz (Sustiva), VL - viral load
OBT - optimized background therapy, CBV - Combivir
Issues to Be Addressed Regarding Virology

- Switch to CXCR4 virus predominance
  - A consequence of selection or mutation?
    - V3 alignment and phylogenetic analyses

- R5 viral resistance to maraviroc
  - Phenotypic and genotypic markers
  - Identification of associated point mutations

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