CCR5 Antagonist Drug Development Issues

FDA Perspective

Presentation Outline

- Summarize recommendations for development of:
  - Antiretrovirals in general
  - CCR5 antagonists, specifically
- Summarize unanswered questions
  - safety
  - efficacy
  - tropism changes and resistance

Development of New Classes of Antiretroviral Agents

- General HIV drug development principles apply
  - HIV RNA and CD4 data through Week 24 for accelerated approval
  - HIV RNA and CD4 data through Week 48 (minimum) for traditional approval
  - Two adequate and well-controlled studies
- Evaluation of class and drug-specific concerns
  - May require additional data and longer follow-up

Indications

- Antiretroviral-experienced patients
  - minimum of 24 weeks of data
- Antiretroviral-naïve patients
  - minimum of 48 weeks of data (all ARVs) with commitment for 96 weeks of follow-up (CCR5 antagonists)

After Proof-of-Concept: Timing of Naïve and Experienced Studies

- Risk/Benefit:
  - Depends on safety: preclinical (including resistance) and clinical data
    - If safety concern present - begin with treatment experienced studies then naïve studies, if appropriate
    - If safety concern absent/minimal - naïve and treatment experienced studies at the same time
- Drug-drug interactions
  - necessary to support coadministration of multiple ARVs for background regimens

CCR5 Drug Development

DAVDP Goal:

- Provide consistent advice on amount and type of information needed for approval **BUT** allow for flexibility in overall development plans

CCR5-Specific Evaluations

- Safety and activity data in mixed/dual (R5/X4) patients
- For all populations (R5 and R5/X4):
  - Stringent adjudication of new AIDS-defining events by independent review committee
  - Class-specific AEs for CCR5 antagonists
    - changes to immune system by blocking endogenous CCR5 receptors
  - Tropism changes
    - impact on disease progression
    - monthly tropism reports to monitor changes, viral load and CD4
  - Stored baseline samples for future analyses

Tropism and Resistance Evaluations

- Loss of virologic response (increased HIV RNA) and have a change in tropism
  - Main considerations - determine if:
    - Coreceptor change occurred
    - Outgrowth of a minor population of virus not detected at screening occurred
    - Resistance to the CCR5 inhibitor occurred (through a mechanism other than a coreceptor change)
    - PI/RTI resistance emerged

Analyses for Tropism Changes R5 to R5/X4 or X4

- In vitro susceptibility to coreceptor inhibitor (phenotype)
- Nucleotide sequence analysis (genotype):
  - gp120 region to identify AA changes that may contribute to tropism change or resistance (potential AA changes verified via site-directed mutagenesis)
  - PR and RT
- Clonal evaluation of virus at screening or baseline and subsequent timepoints to determine if outgrowth of minor population occurred
- Phylogenetic analysis to determine relationship of emerging CXCR4 virus to “original” CCR5 virus

Virologic Failure Follow-up

- At least five year follow-up to obtain long-term data on:
  - HIV RNA
  - CD4
  - tropism
  - Progression to AIDS (number of AIDS-defining events and death)
- Evaluations at least 2-3 times per year

Unanswered Questions

1. What is the impact of tropism changes on
   - safety parameters?
   - virologic success or failure?

2. Is the amount, type, and duration of data sufficient to address safety concerns for tropism changes?
   - What are the feasibility concerns for the five-year follow-up commitment and what mechanisms can be used to ensure sufficient data collection and minimize lost-to-follow-up

3. What is the role of CCR5 antagonists in treatment regimens?
   - Are CCR5's a substitute for PI/NNRTIs; one nRTI vs dual nRTIs?

Tropism and Resistance Questions

4. What resistance/tropism information is needed at the time of approval of new CCR5 antagonists, and how much?
   - Is data from a subset of study subjects acceptable, and if so, from what proportion?
5. In clinical practice will tropism testing be done at screening, post-failure, or routinely?