CCR5 Antagonists: FDA Perspective on Drug Development Issues

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Agenda

Session I: Chemokine Antagonists in Development: Current Status	
Chemokine Receptors and Antagonists: Summary of Clinical Experience	Dr. Roy Gulick
Recap of FCHR Chemokine Antagonist Working Group Meetings	Dr. Veronica Miller
FDA Presentation: Summary of Responses from Industry, Government and Community	Dr. Scott Proestel
Long-term Safety Monitoring	Drs. Dan Kuritzkes and Jens Lundgren
Session II: Panel Discussion and Public Response:	
Panel A: Monitoring & Safety Panel B: Viral Tropism & Resistance Panel C: Clinical Efficacy and Strategy	Dr. Roy Gulick Dr. Joe Eron Drs. Roy Gulick and Joe Eron
Wrap-up	

Outline

- Summarize regulatory requirements for development of:
  - Antiretrovirals in general
  - CCR5 antagonists, specifically
- Introduce issues for further discussion
  - Safety and long-term monitoring
  - Tropism changes and resistance

New Classes of Antiretroviral Agents: Treatment-Experienced Patients

- General HIV drug development principles apply – (Guidance for Industry – October 2002)
  - 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

New Classes of Antiretroviral Agents: Naive Patients

- Antiretroviral-naïve patients
  - minimum of 48 weeks of data (all ARVs) with commitment for 96 weeks of follow-up (e.g.,CCR5 antagonists)

Timing of Naïve and Experienced Studies

- Bottom line = Risk/Benefit
  - Depends on safety: preclinical (including resistance) and clinical data
    - If safety concern is present - begin with treatment - experienced studies, then naïve studies
    - If safety concern absent/minimal - conduct 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

- In addition to 2 adequate and well-controlled studies in the R5 population:
  - Safety and activity data in mixed/dual (R5/X4) patients
- For all populations (R5 and R5/X4):
  - Adjudication of new AIDS-defining events by independent review committee
  - Class-specific AEs for CCR5 antagonists
    - changes to immune system by blocking cellular 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) with a tropism change
  - Main considerations - determine if:
    - Coreceptor change occurred
    - Outgrowth of a minor population of virus not detected at screening
    - Resistance to the CCR5 inhibitor occurred through a mechanism other than a coreceptor change
    - PI/RTI resistance emerged

Virologic Failure Follow-up

- The Division of Antiviral Products has requested at least five-year follow-up for:
  - HIV RNA
  - CD4
  - Tropism
  - AIDS-defining events
  - Death)
    - Evaluations at least 2-3 times per year

Panel 1: Safety and LTFU Questions

- FDA requested 5-year follow-up on subjects with VF in phase 2 and 3 studies.
- Assessments to occur 2-3 times per year for CD4, VL, viral tropism, AIDS-defining illness and death.
- Questions:
  - Include virologic successes in assessment?
  - Duration of 5 years – more or less?
  - Monitoring of additional adverse events, i.e. bacterial infections and malignancies?
  - How to minimize LTFU?
  - Design options to establish relationship between viral tropism and pathogenesis?

Panel 2: Tropism and Resistance Questions

- What proportion of subjects with tropism switches is concerning?
  - +/- CD4 count and VL
- What resistance/tropism information is needed at the time of approval of new CCR5 antagonists, and how much?
  - Are data from a subset of study subjects acceptable, and if so, from what proportion?
- In clinical practice will tropism testing be done at screening, post-failure, or routinely?

Panel 3: Clinical Efficacy/Study Designs

1. How will the CCR5 antagonists fit into the armamentarium of antiretrovirals?
2. Are there special concerns for pediatric development of this class?