FDA/FCHR Collaborative Meeting
Long-Term Safety Concerns Associated with CCR5 Antagonist Development

May 31, 2006

Washington DC

Forum for Collaborative HIV Research

School of Public Health & Health Services

The George Washington University

AGENDA -1

8:30 – 10:30	**Session I: Chemokine Antagonists in Development: Current Status**	**Chair: Debra Birnkrant**
8:30	**Welcome & Introductions**	**Debra Birnkrant**
8:35	**Chemokine Receptors and Antagonists: Summary of Clinical Experience** ✓Tropism assay, tropism changes, and safety issues	**Roy Gulick**
9:05	**Recap of FCHR Chemokine Antagonist Working Group meetings**	**Veronica Miller**
9:20	**Regulatory Perspective** ✓Current Requirements for Approval ✓Proposed Monitoring plans ✓Summary of Responses	**Scott Proestel**
09:50 10:10	**Long-Term Safety Monitoring** ✓ACTG experience ✓Long Term Safety Monitoring in Observational Study Setting	**Dan Kuritzkes** **Jens Lundgren**

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	Session II: Panel Discussion and Public Response	Chairs: Roy Gulick & Joe Eron
10:45– 12:30	Panel A: Monitoring & Safety	**Moderator: Roy Gulick** Panelists: **Judith Millard** **Tom Gegeny** **David Haerry** **Katherine Laessig** **Richard Little** **Howard Mayer** **William Olson** **Paul Skolnik** **Kate Squires** **Robert Yarchoan**

Agenda - 3

1:30 – 3:00	Panel B: Viral Tropism & Resistance	**Moderator: Joe Eron** Panelists: **Stephen Becker** **Richard Colvin** **Lynda Dee** **Steve Deeks** **Jim Demarest** **Wayne Greaves** **John Moore** **Lisa Naeger** **Neil Parkin** **Jonathan Schapiro** **Mani Subramanian**
3:00-4:00	Panel C: Clinical Efficacy and Strategy	**Moderators: Roy Gulick and Joe Eron** Panelists from Panel A & B plus pediatrics **Andy Wiznia**
4:00 – 4:15	**Wrap-up**	

Forum Chemokine Antagonist Working Group

Veronica Miller, PhD

Director

FCHR

Forum for Collaborative HIV Research
Chemokine Antagonist Working Group

- Introduction to the Forum for Collaborative HIV Research
- Introduction to Forum Chemokine Antagonist Working Group
- Goals & Objectives
- Recap of Roundtables #1-3
- Future Plans

Acknowledgments

- Steering Committee:
  - Ben Cheng, Lynda Dee, Bill Freimuth, Wayne Greaves, Roy Gulick, Dan Kuritzkes, Howard Mayer, Veronica Miller, Jeffrey Murray, Neil Parkin, Kimberly Struble
- Sponsor willingness to discuss ongoing drug development programs within the Forum context
- Forum team:
  - Ben Cheng, Becky Griesse, Ipsita Das
  - Website manager: Justin Roby

Support for the Chemokine Antagonist Working Group Roundtables & Public Meeting

- Forum for Collaborative HIV Research
  - With special support from:

  - Webcast of May 31 2006 meeting made possible by grants from:

The Forum for Collaborative HIV Research is a public/private partnership including government agencies, industry, HIV researchers and clinicians, payors, foundations and the HIV patient advocacy community.

Our mission is to facilitate and enhance HIV research.

The Forum Executive Committee

- Government Agencies
  - US DHHS (NIH, CDC, FDA, HRSA), State Department (OGAC)
  - European Regulatory: EMEA
- Industries
  - Abbott, Bayer Diagnostic, Boehringer Ingelheim, Bristol-Myers Squibb, Eurofins-Viralliance, Gilead Sciences, GlaxoSmithKline, Merck, Monogram BioSciences, Panacos, Roche Laboratories, Roche Molecular Systems, Pfizer, Schering-Plough, Tibotec, VIRxSYS
- Payors: Kaiser Permanente
- Academia
  - US and Europe
- Providers
- Patient Advocacy
  - US and Europe
- Foundations & Organizations (Gates, AmFAR, IAS)

Chemokine Antagonist Working Group

- Development of new drugs for HIV remains a priority for HIV community
- Need to engage key players in chemokine antagonist drug development and clinical research
  - Patient community, pharmaceutical & diagnostic industry, regulatory agencies, researchers
- Benefit of cross-sponsor experience in guiding development of this drug class

Chemokine Antagonist Working Group

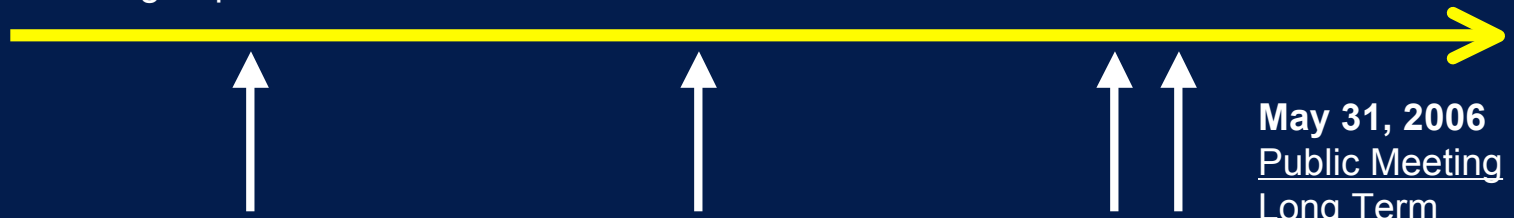
- Provide a neutral, independent platform for discussion of cross-cutting issues in real time
  - New class of drugs: HIV community has limited experience
  - Long-term implications not clear
    - Host receptor involved in immune response
    - Targeting viruses with specified tropism
    - Long term effects of tropic-specific viral inhibition?
    - Lack of experience with tropism diagnostics

Roundtables 1-3

Controversies re
clinical trial design;
Recruitment of treatment
naïve patients to new drug trials
Concerns re driving tropism shift

Aplaviroc:Hepatotoxicity
Class effect?
Mouse CCR5 knock-out
model & FLF

Δ32 & WNV
Vicriviroc:
Malignancies



May 31, 2005
Roundtable 1:
Regulatory Perspective
EMEA & FDA
Clinical Trial Design
Tropism Assay & Change

December 14, 2005
Roundtable 2:
Clinical Developments,
Biology, Immunology

May 30, 2006
Roundtable 3:
Focus on Malignancies
Review of WNV data
Update on hepatotoxicity

May 31, 2006
Public Meeting
Long Term
Follow-up

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Roundtable # 1: Clinical Trial Design & Tropism Diagnosis

- FDA & EMEA Perspectives
  - Trials in treatment naïve patients:
    - FDA: data from closely monitored phase 2b trials if warranted based on earlier safety data
    - EMEA: prefers to defer studies in treatment naïve patients with low CD4 cell counts until Phase 3
  - Long term follow up:
    - FDA: requests 5 years of follow up
    - EMEA: requests 2 years of follow up*

*EMEA currently reviewing regulatory guidance for CCR5 antagonists

RT#1: Long term follow up

- Questions
  - Who?
    - What subset of patients? Control group?
  - What?
    - What data should be collected?
  - How?
    - What mechanisms will support long-term follow up?
    - Patients switching treatment, entering other studies
    - Data harmonization: FDA, EMEA, other countries
- Request for public input
  - FDA/FCHR joint meeting

RT#1: Viral Tropism & Resistance

- Identified key research questions to be addressed in clinical trials and supporting studies
  - E.g.(see report for a full list)
    - Clarify the role of viral tropism in pathogenesis
    - Develop validated guidelines for phenotypic and genotypic resistance testing for CCR5 antagonists
    - Role of pre-therapeutic tropism testing
      - Availability of test
      - Reimbursement
    - Criteria for expanded access?

RT#2: Clinical Developments, Biology & Immunology

- Update on clinical development of the various programs
- Following the report of hepatoxicity observed in aplaviroc development program:
  - Include hepatologists, biologists and immunologists in the working group
  - Review all hepatoxicity related events in clinical trials of all sponsors in the context of combined experience and animal model data (knock-out mouse model data – Swain, 2005)
  - Review of biology & immunology of chemokine and chemokine receptors with reference to chemokine antagonist development
  - Review available data on CXCR4

RT #2: Questions

- Hepatotoxicity – is it a class effect?
- What are some of the potential long-term immunologic effects?
- What are some other biologic effects that should be monitored?
- What lessons can be learned from the potential anti-inflammatory properties?
- Potential effects of individual drugs vs. class

RT#2: Conclusions

- Congenital absence of receptors (k.o. model) may be very different from pharmacological blockade
- Need for careful and detailed data collection in phase 3 trials and expanded access
  - E.g. vaccine responses
- HIV profoundly affects immune system; we are adding another layer of complexity by using a drug that will affect HIV as well as the immune system
- Effects of chemokine inhibition in immunocompromised individuals may be very different from effects in immunocompetent individuals (or in patient with inflammatory disease)
- Challenges re ongoing control arm

Hepatotoxicity & CCR5 Antagonists

- In view of more recent clinical development update (RT#3), hepatotoxicity does not appear to be a class effect

RT #3: Review of West Nile Virus Susceptibility & Incidence of Malignancies

WNV Review

- Animal models and human cohort studies provide evidence that CCR5 receptor involved in West Nile Virus disease susceptibility and disease outcome
- What is the relevance wrt pharmacologic exposure to CCR5 antagonists?
  - Congenital absence vs pharmacologic blockade
  - Need for careful follow-up of patients
    - WNV, other infectious diseases
    - Recommendation to avoid exposure to WNV

RT#3: Review of Malignancies

- A5211 study (vicriviroc exposure):
  - 5 cases of malignancies observed in 118 treatment experienced patients:
    - 1 gastric adenocarcinoma
    - 2 Hodgkin Lymphoma (1 recurrent)
    - 2 Non-Hodgkin Lymphoma (1 with prior Hodgkins)
- Is this a signal? Drug specific or class specific?

RT #3: Review of Malignancies

- Review of clinical trials in similar patient populations
- Review of observational cohort study data
  - EuroSIDA, D:A:D
- Review of other sponsor CCR5 antagonist studies (Pfizer, GSK)

Maraviroc Summary
Malignancy Summary

- Pfizer safety review indicates no evidence of an increased rate of HIV -associated malignancies in the MVC program compared to expected rates based on historical "HAART era" data (EuroSIDA)
- No evidence of an increased rate of unexpected malignancies in this population
- The DSMB has no concern about the rate of malignancies in the program based on any of the data they have reviewed (April 25, 2006)

Incidence in A5211 vs other studies/cohorts

- Overall rate for malignancies appears to be in the range of 4-6 per 100 PYFU
- Overall lymphoma rate appears to be in the range of 1 per 100 PYFU
- Does the rate of lymphomas in A5211 (4 cases total) represent a significant increase?

Biologic plausibility for CCR5 antagonist role in malignancy development

- Hypothetical biologic plausibility
  - Immune surveillance related
    - a-TNF mechanism?
  - Increased chemokine in vitro (in vivo?)
- Biologic plausibility vs. likelihood

Discussion on malignancy/lymphoma

- Need to consider:
  - Tumor heterogeneity
    - HL & NHL are two different diseases
    - Compare “apples with apples”
  - Patient baseline heterogeneity
  - Complex setting; complex epidemiology
    - Duration of infection, duration of treatment of infection
    - Recurrences of lymphomas frequently seen
  - Role of aggressive follow-up and diagnostics
  - The small sample size (A5211)

Malignancy Summary

- The fact that increased rates of malignancy were not observed in other CCR5 antagonist studies does not support a class (or mechanistic) effect
- The fact that 4 cases of lymphoma were observed in one study is of concern to the HIV community but does not warrant stopping development at this time
  - Need for larger studies with appropriate informed consent
  - Need for careful, consistent and thorough follow up of all patients in CCR5 antagonist studies

Forum Chemokine Antagonist Working Group – Future Plans

- Continue meeting every 6 months
- Discuss issues of concern in real time
- Additional topic
  - Role of drugs in prevention
  - Role of genetic heterogeneity (e.g. CCR5 promoter region)
  - Pediatric issues
  - Etc

Future studies

- Companies encouraged to make compound available for in vitro studies
- Continue with epidemiologic analysis of available data