

COLLABORATIVE APPROACHES TO HIV DRUG DEVELOPMENT: PLANNING FOR LONG-TERM MONITORING OF SAFETY IN CCR5 ANTAGONIST DEVELOPMENT

REPORT OF AN FDA/FCHR JOINT PUBLIC MEETING
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The success of the public meeting was in large part dependent on the previously convened series of roundtable discussions sponsored by the Forum Chemokine Antagonist Working Group. The leadership provided by the Working Group's steering committee (see Appendix C) was instrumental in guiding the direction of the Working Group and setting an atmosphere supportive of frank discussion of sponsors ongoing clinical development programs. The sponsors' willingness to discuss their respective ongoing programs over and above the information already in the public domain contributed significantly to the success of this Working Group and the importance of this cannot be overemphasized.

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FDA/FCHR Joint Meeting on CCR5 Antagonist Development

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EXECUTIVE SUMMARY

INTRODUCTION

The Forum for Collaborative HIV Research and the Food and Drug Administration's Division of Antiviral Products jointly sponsored an open public meeting to discuss long term safety issues associated with CCR5 co-receptor antagonists for the treatment of HIV infection.

This open, public meeting followed three roundtable discussions held by the Forum's Chemokine Co-Receptor Antagonist Working Group. The Working Group includes members from US and European regulatory and research sponsoring agencies, pharmaceutical, biotech and diagnostic industry, academic researchers and research networks, and North American and European community representatives. Although these roundtable discussions were not open to the public, information and meeting reports related to these three roundtable discussions are available on www.hivforum.org.

The May 31, 2006 public meeting provided a unique opportunity for open discussion of long term safety concerns between members of each of the relevant constituencies listed above. Specific input from each group was sought prior to the meeting and all participants, including the audience, were able to contribute in panel and discussion sessions.

Long term safety is of concern for each new drug class and each new drug. However, the CCR5 co-receptor antagonists have potential unique safety concerns. The potential selection of X4 tropic viruses and the possible association of X4 tropism with more rapid disease progression is one such concern. Another is the potential effect of CCR5 co-receptor antagonists on the function of the immune system, including susceptibility to infections and potentially impaired immunosurveillance of tumors. Finally, drug resistance may involve escape due to tropism switch (or outgrowth of a pre-existing minor X4 viral populations) as well as traditional drug resistance development.

The main goal of the meeting was to obtain expert discussion on issues relating to viral tropism and safety, feasibility of and best approaches to long term monitoring of adverse effects, and drug resistance. This input will facilitate and promote consistency in the development of these new agents.

FORUM CHEMOKINE ANTAGONIST WORKING GROUP ROUNDTABLES 1-3

The Forum Chemokine Antagonist Working Group was established to provide a neutral, independent platform for discussion of cross-cutting issues in real time, engaging key constituencies involved in CCR5 co-receptor antagonist development for treatment of HIV infection. The benefits of cross-sponsor experience in guiding the development of this drug class, for which we have limited clinical and diagnostic experience, will be of benefit to all members of the HIV community.

Roundtable 1: Clinical trial design and tropism diagnosis (May 23, 2005)

The first roundtable discussion focused on the US and European regulatory requirements, specifically differing views of the appropriate time to initiate clinical trials in treatment naïve patients. Another difference is the length of required follow-up time post study to monitor long term adverse outcomes. Questions that arose during the first roundtable included:

- Who should be followed? What subsets of patients?
 - What is an appropriate control group?
- What data needs to be collected, with what intensity?
- How will long term follow-up be managed?
 - What mechanisms support long-term follow up?
- Is it possible to achieve data harmonization across countries?

Roundtable 1 also identified key research questions to be addressed in clinical trials and supporting studies (see the report on www.hivforum.org for a full list of questions).

Roundtable 2: Clinical developments, biology and immunology (December 14, 2005)

The second roundtable provided an opportunity for the sponsors to update the Working Group on their respective clinical development programs, as well as focusing on an in-depth discussion of the hepatotoxicity observed in the aplaviroc program. Working Group members reviewed all hepatotoxicity related events in clinical trials of all sponsors in the context of combined experience (all sponsors' clinical programs) and animal model data. In addition, the biology and immunology of chemokines and chemokine receptors were reviewed in the context of antagonist development for the treatment of HIV infection. Specific questions that arose during this roundtable include:

- Is hepatotoxicity likely a drug-class effect?
- What are the potential long-term immunologic effects?
- What potential biologic effects warrant monitoring?
- Are there lessons that can be learned from other applications, e.g. anti-inflammatory indications, for these agents?

Although animal models may provide an interesting and useful model to look at some of these questions, congenital absence of a receptor, such in the CCR5 knock-out mouse model, may be very different from a pharmacologic blockade. Careful and detailed data collection in phase 3 and expanded access programs will be required, including, for example, responses to vaccines. In view of more recent clinical development updates (discussed during the 3rd roundtable), the Forum Working Group members agreed that hepatotoxicity does not appear to be a class effect.

Roundtable 3: Review of West Nile Virus susceptibility and incidence of malignancies (May 30, 2006)

Animal models and human cohort studies provide evidence of CCR5 involvement in West Nile Virus disease. In these studies, CCR5 deficiency was associated with an increased risk for symptomatic infection. However, as with hepatotoxicity, the issue of congenital absence of the receptor versus pharmacologic blocking needs to be considered. Careful monitoring of patients for infectious diseases is an absolute requirement.

The issue of malignancies (5 cases recorded in the A5211 study of treatment experienced patients on vicriviroc) was discussed in detail. A review of data from clinical trials in similar patient populations, review of data from observational cohort studies, and review of data from other sponsor CCR5 antagonist development programs provided the context for these discussions. A hypothetical biologic plausibility is presented by the potentially impaired immunosurveillance in patients exposed to CCR5 antagonists. However, biologic plausibility does not necessary imply likelihood. Consideration of the tumor heterogeneity, the patient baseline heterogeneity and advanced HIV disease stage, the complex epidemiology (e.g. recurrence of lymphomas is seen frequently), the role of pro-active diagnostic in the clinical trial setting, and the small sample size are very important in this situation. The fact that increased rates of malignancy were not observed in other CCR5 antagonist studies does not support a class or mechanistic effect. However, the fact that four cases of lymphoma (2 Hodgkin's, 2 non-Hodgkin's) were observed in one study is of concern to the HIV community but does not warrant stopping development at this time. The need for larger studies with appropriate informed consent and for careful, consistent and thorough follow-up of all patients exposed to CCR5 co-receptor antagonist was emphasized.

CONTEXT: CURRENT REGULATORY REQUIREMENTS FOR CCR5 CO-RECEPTOR ANTAGONISTS

The FDA requirements for development of antiretroviral agents in general are described in the Guidance for Industry document (October 2002). The Division of Antiviral Drug Product's goal for CCR5 antagonist development is to provide consistent advice on the amount and type of information needed for approval, but allow for flexibility in the overall development plans. CCR5 antagonist specific evaluations include 2 adequate and well-controlled studies in patients with R5 virus as well as safety and activity data in patients with mixed/dual tropic virus (R5/X4). Adjudication of new AIDS-defining events by an independent review committee is required for all patient populations. In addition, evaluations aimed at assessing class-specific adverse events are requested. Tropism changes along with viral load and CD4 will be reported monthly. Stored baseline samples will be available for future analyses as needed. Tropism and resistance evaluations in cases of loss of virologic control include determination of whether co-receptor

tropism change occurred, whether this is an outgrowth of a minor population not detected at screening, whether non-tropism related resistance developed, or whether virologic failure can be ascribed to viral resistance to the other drugs in the regimen. Furthermore, the Division of Antiviral Products requested at least five years of follow-up (with evaluations 2-3 times per year) for HIV-RNA, CD4, viral tropism, AIDS-defining events, and death for all patients experiencing virologic failure while participating in phase 2 and phase 3 studies.

POTENTIAL MODELS FOR LONG-TERM FOLLOW-UP OF PATIENTS EXPOSED TO CCR5 CO-RECEPTOR ANTAGONISTS

Two models for long-term follow up, different from the proposed long-term follow-up of current CCR5 antagonist trial participants in individual trial (or program) cohorts, were presented:

- Prospective Observational Cohorts
- ACTG Longitudinal Linked Randomized Trials Cohort (ALLRT)

Observational cohort studies traditionally follow patients over a long period of time. Given the fact that randomized long term comparisons of drug regimen have not been conducted in the last decade, cohort studies are the default option. However, the lack of randomization allows for known and unknown confounders to affect specific outcomes. To be useful, cohort studies require carefully designed, prospective data collection, a priori selected endpoints and large sample sizes. The EuroSIDA and the D:A:D cohorts provide ample demonstration of the usefulness of this approach in sorting out specific adverse outcomes, such as cardiovascular disease and liver disease.

The ALLRT cohort study is a unique cohort in that it enrolls only patients (both treatment naïve and treatment experienced) who have participated in ACTG sponsored clinical trials. The primary objective of the ALLRT cohort study is to evaluate the long-term outcomes of potent combination antiretroviral treatment, including virologic, immunologic, pharmacologic and pharmacogenomic, clinical progression, quality of life and resource utilization, as well as neurological and neurocognitive outcomes. The cohort will allow for a prospectively planned series of meta-analyses and cross-protocol analyses. As of May, 2006, the cohort had accrued

3,695 patients. Although this type of study (government sponsored long term follow up) provides a feasible model for long term follow up, specific issues do arise in the context of the long term monitoring needs of the chemokine co-receptor antagonist development program. These include subject and investigator fatigue, low level of usefulness for monitoring a placebo controlled group, and the non-overlapping ALLRT and chemokine co-receptor antagonist clinical trial sites that would complicate the logistics.

DISCUSSION OF SAFETY AND LONG TERM FOLLOW-UP ISSUES

The following questions were presented to panelists and discussed by panelists and members of the audience:

1. The current proposal is to follow subjects who experience virologic failure for five years. Please discuss if all subjects, regardless of virologic success or failure should be followed for five years
2. Please provide recommendations for other potential adverse effects that require additional monitoring such as other bacterial and viral infections and malignancies.
3. What are the feasibility concerns for the five-year follow-up commitment?
4. What mechanisms can be used to ensure sufficient data collection and minimize loss to follow-up?
5. Please discuss design options to further establish the relationship between viral tropism and pathogenesis.

Panel Discussion

- Panelists agreed that all patients, not just those with virologic failure, need to be followed up long term.
 - The usefulness of long term follow-up of patients with virologic failure is reduced by the cross-over design (allowing participants to change from placebo to study drug following virologic failure) which diminishes the control group and generates

bias due to differential length of follow up between those with virologic failure versus those with virologic success.

- The right length of follow-up time cannot be determined at this time.
 - The success of such a program will depend on the composite of follow-up time, sample size and incidence rate of event.
 - The analogy of the tenofovir program, demonstrating the long-term follow up needed for understanding long-term consequences may be useful in this setting.
- Clarity is needed on long-term follow-up of patients currently enrolled in trials versus long-term surveillance and monitoring of adverse outcomes.
 - What are the advantages of post marketing approval studies compared to following patients participating in the trials?
 - A jointly sponsored cohort including patients from the various sponsor's clinical development programs should be considered.
- Long-term follow-up data could be affected by concurrent participation of patients in trials of other investigational agents.
 - Long-term follow-up should be designed in a manner that doesn't negatively affect a patient's ability to participate in trials of other investigational agents.
- The issue of an appropriate control group remains to be resolved.
 - Bias in reporting events generated by the intense follow-up is an issue to be considered.
 - Cross-over and virologic failure decrease the placebo group over time.
- Potential immunologic consequences, including opportunistic infections, unusual infections and reduced tumor surveillance need to be considered.
 - Not known whether any direct immunologic effects will be observed, or whether any observed effects will be permanent or, conversely, whether the effect will be a temporary interference during the actual drug exposure. At present, there are no data or biologic basis to suggest a permanent effect.
 - All events (not just AIDS-defining) need to be collected.
- Cohort studies are useful for picking up major effects; they are not useful for picking up subtle effects.

- The potential impact of viral tropism changes is difficult to predict at this time as the implications for pathogenic consequences are not clear.
- Malignancies surveillance can be simplified given an appropriate control group, but experience in post-combination antiretroviral treatment era has demonstrated that the study of malignancy epidemiology is a moving target.
- The currently evolving clinical data will inform specific questions in order to be able to design the appropriate studies.
- Studies addressing the potential impact of tropism switch need to be well controlled, with specific and focused questions.
 - Patients exposed and not exposed should be followed over time, looking at tropism switch as a time dependent variable.
 - Better use of control arm in naïve studies needs to be considered.
 - Establish and follow a similar cohort on optimized background therapy without CCR5 antagonist exposure to look for consequences of tropism switch.

DISCUSSION OF RESISTANCE AND TROPISM ISSUES

The following questions were presented to panelists and discussed by panelists and members of the audience:

1. What degree of tropism change, for example, in an individual or in what proportion of subjects, would be cause for concern? Please consider this in both the presence and absence of effects on CD4+ cell count and viral load.
2. What resistance/tropism information is needed at the time of approval of new CCR5 co-receptor antagonists, and how much? Are data from a subset of study subjects acceptable, and if so, from what proportion?
3. What is the role of tropism/resistance testing in clinical practice (e.g. routine, optional, none?)

Panel Discussion: Significance of changes in viral tropism

- The field is now at a similar point with respect to viral tropism, changes in tropism and the potential clinical impact as it was at the time when the roles, contributions and impact of CD4 and viral load were being elucidated.
- The precise definition of switch is not clear: what is the threshold of clinical significance?
- It is clear that major switch issues have not been observed to date in clinical trials
- Frequently the X4 signal is very low (sub-threshold levels) yet real: does this have clinical significance?
- Tropism changes back and forth from R5 tropic to X4 tropic or mixed/dual tropic virus and vice-versa are frequently observed (in about 10% of patients) in the absence of CCR5 antagonist exposure, including in patients on combination antiretroviral therapy.
 - Any study designed to assess the role of tropism switch for pathogenesis will need to take this into account.
- Two questions need to be distinguished: the effect of tropism on CD4 cell count and viral load (or the pathogenesis related issues) and the issue of tropism switch as a mechanism of viral escape (or the drug resistance issue).
- Two scenarios should be distinguished:
 - enrichment of X4 tropic virus coincident with CCR5 antagonist exposure which is reversed upon discontinuation of the drug is probably of less concern than if the changes remain after discontinuation
 - any impact of X4 enrichment on viral load or CD4 cell count would affect the risk:benefit balance, and even a low incidence of such events would have an impact
 - if there is an effect on CD4 cell count, the slope of decline over time should be followed
- Although it is difficult to specifically advise the agency at this time, tropism switches in the absence of viral load or CD4 effects would likely not seem to be important.
- The causal nature of the relationship between X4 tropic virus and HIV pathogenesis is not clear:

- arguments to support both directions are available, but this question cannot be answered at this time
- it is possible that both directions are relevant
- it is possible that consequences will be different for naïve versus experienced patients

Panel Discussion: Diagnostic issues

- Confusion exists regarding what the currently used diagnostic assays demonstrate.
- Historically, more familiarity exists between the syncytium-inducing (SI) and non-syncytium-inducing (NSI) assay in the context of natural history studies, but this assay is no longer used.
 - SI and NSI implications for pathogenesis have not been studied in patients on treatment
- Currently, researchers are attempting to assess the clinical significance of “blips” of X4 tropic virus detection without natural history studies to provide context.
- Clarity is needed on whether it is an issue of *relative* increase or *absolute* increase in X4 tropic viruses:
 - a *relative* increase of X4 tropic virus would not be as significant (simply a matter of an increased chance of detection) as an *absolute* increase (indicating a potentially preferential expansion of this viral population)
 - In the available tropism assay, inhibition of R5 virus by a CCR5 antagonist would be expected to increase detection of X4 virus, even in the absence of any absolute increase in the amount of X4 virus

Panel Discussion: Drug resistance

- The FDA would like to know: why are people failing, what is the predominant reason for virologic failure? Reasons for failure include:
 - Outgrowth and/or switch (the consequence possibly would be no response to other drugs in this class) due to
 - undetected X4 tropic virus at baseline,

- actual switch (evolution to new tropism)
 - “Classic” drug resistance to antagonist
 - Resistance to other drugs in the regimen
- To answer these questions, appropriate data is required, including clonal analysis of viral populations at baseline
- The cost and resource intensive nature of the required studies need to be recognized
 - How many patients do we need to be able to answer these questions?
- Specific advice on the number of patients that need to be studied cannot be provided at this time, given our limited knowledge.
 - The envelope region of HIV is a complicated region, with great variability between patients
 - Viral clonal analyses are absolutely required in clinical trials
- The field will benefit if resistance related information, reagents and isolates are shared across companies and with collaborators

Panel Discussion: Use of assay

- In treatment naïve patients, a tropism diagnostic assay likely will be essential to identify suitable candidates for CCR5 antagonist treatment in order to minimize the risk to other drugs in the regiment, should the patient have X4 tropic viruses
- Monitoring at time of failure may be important if switch is associated with adverse outcome

CLINICAL EFFICACY STUDY DESIGN & PEDIATRIC ISSUES

The following questions were presented to panelists and discussed by panelists and members of the audience:

1. How will the CCR5 antagonists fit into the antiretroviral armamentarium?
2. Given the issues previously discussed are there any special/additional concerns for pediatric drug development?

Panel Discussion: CCR5 in antiretroviral armamentarium

- In cases where active agents are available from multiple treatment classes, safety is the most important feature determining what agents are used.
- Combining compounds within the drug-class and with drugs in other classes is of great interest.
- The greatest need for new classes of drugs, with new mechanisms of action, is in treatment-experienced patients who have resistance to currently available drugs.
 - In advanced disease, up to 50 percent of patients have dual/mixed virus, which negatively impacts the virologic activity of CCR5 antagonists, underscoring the potential need for tropism testing.
- In treatment-naïve patients, currently available regimens present a higher barrier to a new class of drugs:
 - Current regimens are efficacious, convenient, safe, and with manageable drug-drug interactions in most patients, but there remains room for improvement
 - The fact that 80% to 90% of treatment-naïve patients have CCR5-tropic virus makes CCR5 antagonists an appealing potential treatment option.
 - CCR5 inhibitors, if safe, may serve niche populations:
 - women of child-bearing potential
 - people with non-nucleoside reverse transcriptase inhibitor resistant virus
 - patients who are intolerant to side effects of non-nucleoside reverse transcriptase inhibitors
- CCR5 antagonists may also play a role in treating acute infection, in pre- and post-exposure prophylaxis, and as active components in microbicides.

Panel Discussion: Pediatric Issues

- Novel agents approved for use in adults, are anticipated to be widely used in children.
- The number of babies and younger children with HIV (in the developed world) is low and is anticipated to decrease due to routine testing for HIV during pregnancy.

- Most pediatric patients with AIDS are pre-teens, many of them have moved through sequential therapies, including multiple combination antiretroviral regimens.
- Some children have had to withdraw from some treatments due to toxicities.
- Some pediatric patients have fully controlled HIV replication with treatment, while others have highly resistant HIV.
- Pre-teens and teenagers with multi-drug resistant virus have a compelling need for a new drug-class
- For a heavily treatment-experienced pediatric population with few treatment options and a fair amount of off-label drug use, the FDA would entertain various types of protocols, even prior to approval, including a written request for a sponsor to obtain pediatric exclusivity.
 - Once a drug is approved for adults, the Pediatric Research Equity Act would require pediatric studies.
 - Phase 2 trials in adults may provide adequate data for initiating pediatric phase 3 trials parallel with adult phase 3 trials. It was also suggested that in phase 2 trials in adults, exclusion criteria may be extended to include adolescents.
- Long-term follow-up in children, in trials and in general in clinical practice, is challenging, and for safety, requires the development of plans to manage entrance into adolescence and adulthood.
- Obtaining data on pharmacokinetics, toxicity, and activity of CCR5 antagonists in children, particularly adolescent and peri-adolescent children, is imperative.
- Planning for pediatric therapeutic trials should be started sooner rather than later:
 - Such planning would benefit from knowing the efficacy of CCR5 antagonists in patients with dual/mixed virus.
 - Short- and long-term toxicity and adverse events in pediatric patients is unknown currently.
- It would also be of interest to know:
 - the size of the pediatric population with drug-resistant HIV who would be candidates for CCR5 antagonists, as well as other drug-classes, and
 - what proportion of children have CCR5-tropic, CXCR4-tropic, or dual/mixed virus

- Immunologic response to a recall antigen in children receiving a CCR5 antagonist compared to a control group of children not receiving a CCR5 antagonist should be assessed:
 - Specifically, sustainability of titers should be compared.

INTRODUCTION

On May 31, 2006, a collaborative meeting was organized to allow an open discussion between regulatory agencies, pharmaceutical and diagnostic companies, academia, and the community about the numerous challenges regarding the development of CCR5 antagonists, a new class of compounds for treatment of HIV infections. A public meeting was particularly important because this class of compounds may have unique safety concerns. One potential issue is that CCR5 antagonists may select for X4 viruses and there is concern that this may be associated with more rapid disease progression. Effects of chronic CCR5 antagonist administration on the immune system are unknown, necessitating the need for prospective, long-term safety monitoring. In addition, resistance mechanisms may be complex for these compounds and thus require additional testing. This public meeting followed three closed roundtable discussions convened the Forum for Collaborative HIV Research (FCHR) (see below).

The FDA-FCHR public meeting consisted of 2 sessions: the first session dealt with the current status of CCR5 antagonists in development, and the second session consisted of 3 discussions among a panel of experts and the responses of an audience of experts, on 1) drug monitoring and safety, 2) viral tropism and resistance, and 3) clinical efficacy and strategy (See Agenda, Appendix A; Moderators, Presenters and Panelists, Appendix B).

CCR5 ANTAGONISTS: FDA PERSPECTIVE ON DRUG DEVELOPMENT ISSUES

For accelerated approval of HIV drugs for treating treatment-experienced patients, the FDA requires supportive data on HIV RNA levels and CD4+ cell counts through week 24 of treatment, followed by data through at least week 48. For traditional approval, 48-week data is required. A statutory requirement of substantial evidence is sought from 2 adequate and well-controlled studies in patients infected with the CCR5-tropic strain of HIV, as well as safety and activity data from patients infected with the CCR5/CXCR4-tropic (dual/mixed) strain of HIV. If through phase 3 studies drug- and drug class-specific concerns arise, additional data and longer follow-up may be required. For approval of HIV drugs for treating treatment-naïve patients, the FDA requires a minimum of 48 weeks of follow-up with a commitment for at least 96 weeks of follow-up. Various treatment options do already exist for treatment naïve patients, thus the concern is greater for this population compared to treatment experienced patients with fewer options. If safety concerns are identified in preclinical and clinical studies (including resistance), the FDA asks companies to begin studies in treatment-experienced patients first. Otherwise, studies in treatment-experienced and treatment-naïve subjects may proceed simultaneously. For all patients (with CCR5- and CCR5/CXCR4-tropic viruses), the FDA requires the following: adjudication of new AIDS-defining events by an independent review committee; reports of drug class-specific adverse events, including any effects on the immune system; 2-3 times yearly reports of tropism changes, viral load, CD4+ cell counts, and impact on disease progression; and storage of baseline samples for future analyses.

Additional topics of interest discussed during this meeting include: potential loss of virologic response (an increase in HIV RNA) associated with a viral tropism change, potential cross-resistance within the drug class, development of drug resistance in association with, or independent of, tropism change, if so, whether it is an outgrowth of a minor population of virus that was not detected at baseline screening; and whether protease inhibitor /nucleoside reverse transcriptase inhibitor resistance emerged. For patients exhibiting virologic failure, the Division of Antiviral Products of the FDA has requested the following evaluations at least 2 to 3 times per year for at least 5 years: HIV RNA, CD4+ cell counts, tropism, AIDS-defining events over time, death, and evaluation of these items.

CHEMOKINE RECEPTORS AND ANTAGONISTS: SUMMARY OF CLINICAL EXPERIENCE

CCR5 antagonists belong to the chemokine co-receptor antagonist drug class. They inhibit HIV entry into the cell by blocking the binding of HIV to its co-receptor (in this case, CCR5) on the cell surface.¹ CCR5 antagonists of clinical interest include maraviroc, vicriviroc, PRO 140, and TAK 652. Several issues are relevant in the clinical development of CCR5 inhibitors: the determination of entry tropism and what it means in terms of the pathogenesis of AIDS; compound- and drug class-specific immunologic consequences of viral tropism; compound- and drug class-specific toxicities; antiretroviral activity in treatment-naïve versus treatment-experienced patients; drug resistance; and long-term follow-up.

The entry tropism assay currently in use is available from Monogram Biosciences. The assay has a turn-around time 14 to 18 days, fails to work in 3%-7% of patients, and requires at least 1,000 copies/mL of HIV RNA. The assay was 100% effective in detecting model CXCR4-tropic or dual/mixed HIV present in a 10% mixture, and 83% effective at a 5% mixture. Using this assay, overall, in studies including hundreds of treatment-naïve patients, 80% to 90% of infections were identified as being with CCR5-tropic virus only, and 12% to 20% dual/mixed virus; infection with only CXCR4-tropic virus is rare. However among heavily treatment-experienced patients, about half of infections are with only CCR5-tropic virus, with the other half primarily dual/mixed viruses, suggesting that tropism shift may occur with treatment. Although the switch from CCR5- to CXCR4-tropic virus is temporally associated with increased disease progression and a more rapid loss of CD4+ cells, leading to concerns that CXCR4-tropic viruses may be more pathogenic, it is not clear that the tropism switch is indeed the cause for this progression.²

Studies of people with the CCR5 Δ 32 deletion mutation may provide a hint of what consequences the blocking of this chemokine receptor would lead to. The CCR5 Δ 32 allele is believed to have originated in Europe: it occurs in 5% to 14% of European Caucasians, and about 1% of Europeans have a homozygous genotype. Its emergence in Europe may be related to outbreaks of smallpox or plague. The CCR5 Δ 32 allele is associated with less joint inflammation and morning stiffness in rheumatoid arthritis;³ it may⁴ or may not⁵ be less common in patients with asthma, or have no association with asthma; it is less common in patients with Kawasaki disease;⁶ and there

is debate over its effects on sclerosing cholangitis,⁷ and organ transplant survival.⁸ CCR5Δ32 has been reported to be more common in patients with Hepatitis C infection,⁹ although others disagree;^{10 11} and is associated with lower inflammation and fibrosis and clearance of viremia.¹² Similarly, in mice, CCR5 deletion is associated with fulminant liver failure following ConA administration,¹³ and with exacerbation of T-cell mediated hepatitis.¹⁴ Another recent study reports that CCR5Δ32 is associated with increased severity and mortality of West Nile Virus infection.¹⁵ CCR5Δ32 is also associated with a 3-fold lower risk of AIDS-related Non-Hodgkin's lymphoma.¹⁶ Several studies report that CCR5Δ32 is protective in HIV infection: heterozygous patients have reduced HIV disease progression compared with people without the allele, and homozygous patients are relatively resistant to HIV infection.¹⁷ However, pharmacological blocking of CCR5 receptors is not the same as a congenital absence of this receptor; thus, the extent to which these studies are relevant to the use of chemokine receptor antagonists in the treatment of HIV infection is not known.

Several CCR5 small molecules inhibitors have been designed.¹⁸ Schering C was the first drug to reach studies in humans, but after a phase 1B trial, its development was abandoned due to drug-induced QT interval prolongation. The development of aplaviroc (873140) was discontinued due to drug-induced hepatotoxicity, including 4 cases of clinically relevant hepatotoxicity in treatment-naïve patients in phase 2B trials and 1 case in a treatment-experienced patient in a phase 3 trial. Other small molecule inhibitors currently in late stages of clinical development are maraviroc and vicriviroc.

Maraviroc is the first of these CCR5 antagonists to have reached advanced clinical development. Maraviroc monotherapy has demonstrated efficacy in a phase 2A study in asymptomatic patients: it resulted in a 1.6 log reduction in viral load level over 10 days, and the antiviral effect was prolonged.¹⁹ In phase 1 and 2A trials, including more than 500 HIV-negative and more than 65 HIV-positive patients treated with maraviroc, at doses <300 mg BID, adverse events were similar to those seen with placebo, and with a daily dose of <600 mg, no cases of orthostatic hypotension were observed. Sporadic cases of clinically relevant elevated transaminase levels were documented, but these cases showed no dose relationship and no associated with elevated bilirubin levels. There was no evidence of clinically relevant drug-related prolongation of QT

interval. In November 2005, 1 case of hepatotoxicity was reported in a patient with a complicated history and on other hepatotoxic medications.²⁰ As of May 2006, more than 2,100 subjects were enrolled in phase 2B/3 maraviroc studies: 908 treatment-naïve patients with R5 virus in study 1026, 601 and 474 treatment-experienced patients with R5 virus in studies 1027 and 1028, respectively, and 190 treatment-experienced patients with dual/mixed virus in study 1029. An independent Data Safety Monitoring Board (DSMB) has recommended stopping the 300 mg QD dose and continuing the 300 mg BID dose in study 1026 of treatment-naïve patients. The DSMB also noted that the incidence of malignancy was consistent with known rates in the general population, and recommended continuation of these studies.

Vicriviroc is the next CCR5 antagonist to have reached clinical development. In a phase 2A study of monotherapy in patients with R5 virus off antiretroviral medication, the highest dose of vicriviroc was associated with approximately 1.6 log reduction in viral load over 14 days.²¹ Another phase 2 study was conducted in 17 sites in the US and Canada enrolling 92 treatment-naïve patients with R5 virus and no baseline resistance mutations.²² Patients received placebo or vicriviroc monotherapy at doses of 25, 50, or 75 mg daily for 2 weeks, followed by the addition of zidovudine plus lamivudine to each vicriviroc regimen, or efavirenz plus zidovudine plus lamivudine. Treatment with vicriviroc resulted in a 0.9 to 1.3 log greater decrease in viral load over 14 days, compared with no change in the control group. However in longer-term follow-up, up to 56% of patients treated with vicriviroc exhibited a rebound in viral load to >50 copies/ μ L, compared with only 4% in the efavirenz group. The DSMB recommended stopping the study due to suboptimal antiviral activity. In these trials of vicriviroc, no seizures were reported; the seizure threshold is thought to be 10- to 20-fold higher than the threshold observed in animals. No cases of hepatotoxicity were observed. Additional safety reports included 3 cases of serious adverse events and reports of mild-moderate headache, diarrhea and nausea; however, no change in electrocardiogram or cardiac rhythm, and no clinically significant changes in lab values were observed.

A phase 2 study, ACTG 5211, was begun in 118 heavily treatment-experienced patients failing a ritonavir-containing regimen. Treatment consisted of adding vicriviroc at doses of 5, 10, or 15 mg plus ritonavir therapy (vs. placebo) for 2 weeks, and then optimizing background

antiretroviral therapy based on resistance testing, and continuing treatment for 46 weeks. The endpoints were change in HIV RNA through 14 days and 24 weeks, safety/tolerability, durability of HIV RNA response, and resistance. On October 14, 2005, the Study Monitoring Committee recommended stopping the lowest dose (5 mg) on the basis of the Schering-Plough study in treatment-naïve patients and on the finding of co-receptor use changes. Five malignancies arose in patients taking vicriviroc: 2 cases of Hodgkins lymphoma (1 in a patient with a history of treated Hodgkins disease thought to be in remission), 2 cases of non-Hodgkins lymphoma (1 with a history of treated of Hodgkins disease thought to be in remission), and 1 case of gastric adenocarcinoma. Causality could not be established. In this study, virologic activity and CD4+ cell count responses were seen with vicriviroc.²³

Three cases of changes in co-receptor tropism have been reported in the maraviroc program.²⁴ After 10 days of treatment with maraviroc in patients with only R5 virus, no change in co-receptor phenotype was observed in 60/62 patients. In the other 2 patients, at day 11, CXCR4-tropic viruses were detected. However, in 1 of the 2 patients, at 40 days after ceasing maraviroc treatment, the circulating virus population reverted to R5 phenotype. The other patient continued to have dual/mixed virus and exhibited a decline in CD4+ cell count (593 to 219) over a year; 433 days after coming off the study, this patient started other antiviral treatment. A third patient had dual/mixed virus at baseline and entered the study due to a screening error. This third patient exhibited a transient increase in the CXCR4 component during therapy and no change in HIV RNA level. It was concluded that CXCR4-tropic variants emerged from a pre-existing reservoir, not from a co-receptor use change.

Overall, there have been 6 reported cases of co-receptor tropism changes with CCR5 antagonist treatment: 1 case with aplaviroc 200 daily, 3 cases with maraviroc 100 mg twice daily or daily, and 2 cases with the high dose of vicriviroc. In general, these appear to be due to an emergence of pre-existing CXCR4-tropic strains not detected at baseline.

In vitro studies have provided extensive information on resistance, demonstrating that resistance to CCR5 antagonists occurs independent of tropism change.²⁵ Drug resistance mechanisms may involve the ability of HIV to bind the CCR5 inhibitor-receptor complex.²⁶ Resistance to CCR5

antagonists has been associated with increased affinity for CCR5,²⁷ changes in the gp 120 V3 loop,^{28,29,30,31} and with other gp 120 (or other envelope) changes.³² One study found that maraviroc-resistant isolates were not cross-resistant to other small molecules in the class: aplaviroc, vicriviroc, or SCH-C.³³ Clinical information on resistance to CCR5 antagonists is sparse. In the vicriviroc study in treatment-naïve patients, changes in the IC₅₀ (the concentration required to inhibit viral replication in vitro by 50%) did not explain viral rebound.³⁴

In summary, SCH-C has been withdrawn due to QT prolongation, and aplaviroc due to hepatotoxicity. Maraviroc is currently being studied in phase 2/3 clinical trials in treatment-naïve and treatment-experienced subjects with CCR5-tropic virus. These trials are fully enrolled and in active follow-up. Another trial of maraviroc in subjects with dual-mixed virus is also fully enrolled and in active follow-up. In the trial in treatment-naïve patients, the 300 mg QD arm was terminated due to suboptimal antiretroviral activity. The two cases of severe hepatotoxicity observed with maraviroc were most likely not related to study-drug. Vicriviroc is currently being studied in the phase 2 ACTG trial in treatment-experienced subjects. This trial is fully enrolled and in active follow-up. A study in treatment-naïve subjects was stopped due to suboptimal antiretroviral activity compared to a traditional regimen including efavirenz. Four cases of lymphoma were reported in the ACTG A5211 trial, although causality could not be established.

Two other CCR5 inhibitors in development are TAK-652, another small molecule, and PRO 140, a monoclonal antibody. Both have reported results of trials in HIV-negative volunteers.^{35 36} A phase 1 PRO 140 study in HIV-positive patients has begun.³⁷ Recently, PRO 140 was granted Fast Track Status by the FDA.³⁸

Issues in development of CCR5 antagonists include the following: determination of viral co-receptor tropism; co-receptor tropism changes and potential effects on viral pathogenesis; potential compound- and drug class-specific immunologic consequences, such as opportunistic infections and malignancies; and potential compound- and drug class-specific toxicities, such as QT prolongation and hepatitis. Other issues common to development of all antiretroviral drugs include activity in treatment-naïve and treatment-experienced patients; resistance; and long-term follow-up.

SUMMARY OF THE PREVIOUS THREE CLOSED ROUNDTABLE MEETINGS

The FCHR is a public/private partnership whose mission is to facilitate and enhance HIV research. The Executive Committee of FCHR includes members from government agencies in the US³⁹ and Europe,⁴⁰ industries,⁴¹ payors,⁴² academia in the US and Europe, providers, patient advocacy groups in US and Europe, and Foundations and Organizations.⁴³ The Chemokine Co-Receptor Antagonist Working Group of the FCHR is supported through private⁴⁴ and public funds,⁴⁵ and the free web-cast of the FDA-FCHR public meeting, with grants from industry.⁴⁶ Three roundtable discussions have been sponsored to date, followed by the FDA-FCHR public meeting.

The Forum Chemokine Co-Receptor Antagonist Working Group was established to provide a neutral, independent platform for discussion of cross-cutting issues in real time, engaging key constituencies involved in CCR5 co-receptor antagonist development for treatment of HIV infection. The benefits of cross-sponsor experience in guiding the development of this drug class, for which we have limited clinical and diagnostic experience, will be of benefit to all members of the HIV community. Although the roundtables were not open to the public, information (including agenda and presentations) regarding this series of meetings is available at www.hivforum.org.

ROUNDTABLE 1: Clinical trial design and tropism diagnosis (May 23, 2005)

The May 31, 2005 roundtable was convened after the initial efficacy studies of CCR5 antagonists, when controversies regarding clinical trial design and the recruitment of treatment-naïve patients to new drug trials arose, and concerns regarding consequences of tropism shift were voiced. This first roundtable focused on the US and European regulatory perspectives, clinical trial design issues specific to this drug class, tropism diagnostic assays, and implications of tropism change. For trials in treatment-naïve patients, the FDA requires data from closely monitored phase 2B trials, if warranted, based on earlier safety data. The European Agency for the Evaluation Medicinal Products (EMA) prefers to defer studies in treatment-naïve patients with low CD4+ cell counts until phase 3. The FDA requests 5 years of follow-up, and the EMA requests 2 years of follow-up, although the EMA is currently reviewing regulatory guidance for

CCR5 antagonists. The following questions remain regarding long-term follow-up: Who should be followed up? What data should be collected? What mechanisms would support long-term follow-up? How should patient switching treatment be handled? How could data from different sources be harmonized? Regarding viral tropism and resistance, key research questions were identified: What is the role of viral tropism in pathogenesis? How can validated guidelines be developed for phenotypic and genotypic resistance testing for CCR5 antagonists? What is the role of pre-therapeutic tropism testing? What should be the criteria for expanded access?

Roundtable 1 also identified key research questions to be addressed in clinical trials and supporting studies (see the report on www.hivforum.org for a full list of questions).

ROUNDTABLE 2: Clinical developments, biology and immunology (December 14, 2005)

The December 14, 2005 roundtable was convened following reports of aplaviroc hepatotoxicity, which resulted in withdrawal of this investigational compound from development. The immediate concern was whether hepatotoxicity is a drug-class effect. Coincidentally, publications of animal model studies demonstrating fulminant liver failure in the CCR5 knockout model appeared as this roundtable was being planned. Topics discussed in Roundtable 2 were updates of clinical developments, biology, immunology, and hepatotoxicity. This working group included hepatologists, as well as biologists, and immunologists. Working Group members reviewed all hepatotoxicity related events in clinical trials, in the context of the knockout mouse model data, the biology and immunology of chemokine and chemokine receptors with reference to chemokine antagonist development, and available data on CXCR4 compounds. The questions discussed included: Is hepatotoxicity a class effect? What are the potential long-term immunologic effects of this drug class? What biologic effects should be monitored? What can be learned from the potential anti-inflammatory properties? It was concluded that congenital absence of CCR5 may be very different from pharmacologic blockade. The need for careful and detailed data collection in phase 3 trials and expanded access was clearly stated. Chemokine antagonists may directly and indirectly affect the immune system via effects on HIV. The effects of chemokine inhibition in immunocompromised patients may be very different from effects in immunocompetent patients, or in patients with inflammatory disease. In trials, keeping an

ongoing control arm may be a challenge. Regarding hepatotoxicity, in view of more recent clinical developments update, discussed in roundtable 3, hepatotoxicity does not appear to be a class effect.

ROUNDTABLE 3: Review of West Nile Virus susceptibility and incidence of malignancies (May 30, 2006)

The May 30, 2006 roundtable occurred after publication of increased susceptibility to West Nile Virus in people with the CCR5 Δ 32 deletion mutation, and 5 cases of malignancy in patients taking vicriviroc in the ACTG 5211 study. Topics discussed were malignancies with CCR5 antagonists, the West Nile Virus data, and an update on hepatotoxicity. Regarding West Nile Virus, animal models and human cohort studies provide evidence that the CCR5 receptor is involved in disease susceptibility and outcome. However, the relevance of pharmacologic exposure to CCR5 antagonists is unclear. Nevertheless, careful follow up of patients receiving chemokine antagonists is required.

To provide a context for the discussion of malignancies, the Working Group reviewed data from clinical trials in similar patient populations, data from observational cohort studies and data provided by the sponsors of CCR5 antagonist development programs. Although a hypothetical biological plausibility is presented by the potentially impaired immunosurveillance in patients exposed to CCR5 antagonists, biological plausibility does not necessarily imply likelihood. Consideration of the tumor heterogeneity, the patient baseline heterogeneity and advanced HIV disease stage, the complex epidemiology (e.g. the recurrence of lymphomas is seen frequently), the role of pro-active diagnostics in the clinical trial setting, and the small sample size are very important in this situation. Furthermore, the fact that increased rates of malignancy were not observed in studies of CCR5 antagonists other than vicriviroc, supports the conclusion that a class (or mechanistic) effect is unlikely, and does not warrant stopping development at this time. The findings do, however, point to the need for larger studies with appropriate informed consent. There is also a need for careful, consistent and thorough follow up of all patients in CCR5 antagonist studies.

FDA/FCHR Joint Meeting on CCR5 Antagonist Development

The Chemokine Antagonist Working Group plans to continue meeting every 6 months. Additional topics to be addressed are the potential role of drugs in prevention (for example, as active components in microbicides); the role of host genetic heterogeneity, for example in the CCR5 gene promoter region; pediatric issues; and any other issues that arise.

SUMMARY OF RESPONSES FROM INDUSTRY SPONSORS AND COMMUNITY GROUPS REGARDING THE DEVELOPMENT OF CCR5 ANTAGONISTS

The FDA posed questions to industry sponsors, patient advocacy groups, and other government organizations⁴⁷ regarding the development of CCR5 antagonists and requested responses prior to the public meeting. Five sets of questions were addressed, on 1) safety and tropism issues, 2) long-term monitoring, 3) the role of CCR5 antagonists in the approved anti-retroviral armamentarium, 4) the potential role of tropism and resistance testing in clinical practice, and 5) concerns for pediatric drug development. The responses to these questions are summarized below.

The responders comments reflected the overall discussion as summarized above. Long-term monitoring received the most attention. The FDA requests 5-year follow-up of patients with virologic failure. This is anticipated to be a post-marketing commitment for approved CCR5 antagonists. The challenges of 5-year follow-up include loss to follow up due to the loss of interest of patients and sites, a mobile society, and difficulty complying with multiple protocols; subsequent exposure to additional therapies; and distinguishing treatment-naïve and treatment-experienced patients. Differentiating the effect of the original CCD5 antagonists treatment from subsequent exposure to additional therapies will be a challenge, especially in discerning the treatment effects in treatment-experienced patients.

The following mechanism were suggested to ensure sufficient long-term data collection: prospective enrollment for long-term follow-up; use of settings where patients already receive their medical care; minimizing burden of follow-up by focusing on the topic of interest; using sites that have demonstrated commitment to continuity of care; using established observational cohorts; ensure “buy-in” from patients and investigators; providing a prospective plan for following patients who move; and assessing patients with other diseases, such as rheumatoid arthritis, in whom immunosuppression may be more readily detected.

Appropriate long-term data include viral load, CD4+ cell count, AIDS-defining illnesses, non-HIV related infections, malignancies, and survival. Viral tropism testing may be needed to

exclude patients with CXCR4-tropic virus, but routine tropism testing is not recommended because of it has a long turn-around time, it is expensive, not quantitative, cannot identify tropism species at low proportion, and it has no established clinical predictive value. CD38 measurements for T cell activation may also be useful. The role of resistance testing is unclear. It may be difficult to define a threshold for phenotypic or genotypic resistance prior to approval. There are no specific immunologic parameters to follow during clinical trials that might help monitoring for infection or malignancy.

Responses to the remaining questions were less extensive. The clinical role of CCR5 antagonists will be determined by clinical trials that provide the basis for approval. Theoretically, CCR5 antagonists may be more beneficial in treatment-naïve patients or as prophylaxis in post-exposure patients, who would be expected to have a higher proportion of CCR5-tropic virus. It is unknown whether CCR5 inhibition would affect the developing immune system or response to vaccines in children. Therefore, pediatric studies of CCR5 antagonists should be limited to children who are highly treatment-experienced, have CCR5-tropic virus, and limited treatment options. Study designs deemed inappropriate by the HIV community include the use of suboptimal therapy, specifically prolonged monotherapy; restrictions placed on subsequent treatment; and termination of therapy upon study completion.

MODELS FOR LONG-TERM SAFETY MONITORING

Two models for long-term follow up, different from the proposed long-term follow-up of current CCR5 antagonist trial participants in individual trial (or program) cohorts, were presented:

- Prospective Observational Cohorts
- ACTG Longitudinal Linked Randomized Trials Cohort (ALLRT)

Observational cohort studies traditionally follow patients over a long period of time. Given the fact that randomized long term comparisons of drug regimen have not been conducted in the last decade, cohort studies are the default option. However, the lack of randomization allows for known and unknown confounders to affect specific outcomes. To be useful, cohort studies require carefully designed, prospective data collection, a priori selected endpoints and large sample sizes. The EuroSIDA and the D:A:D cohorts provide ample demonstration of the usefulness of this approach in sorting out specific adverse outcomes.

KEY LESSONS FROM LONG-TERM SAFETY MONITORING OF PATIENTS IN AN OBSERVATIONAL SETTING

Observational studies provide a potential opportunity to monitor long-term safety, although the advantages and disadvantages presented by cohort studies and randomized clinical trials need to be considered.

The advantages of using observational studies to assess long-term safety of antiretroviral therapy include the following: cohort studies are designed to follow patients long-term; they allow for assessment of incidence of outcome and of risk factors affecting outcome; they can place safety issues into perspective and address potential risk/benefit ratio. Cohort studies can also be used to develop criteria for future testing of a probable cause, based on reproducibility, doubling of risk outcome, and biological plausibility. Methodology for controlling for confounders exists; however, the lack of randomization allows for confounders to affect outcome, which compromises the ability to assess causal relationships.

Cohort studies require carefully designed, prospective data collection, *a priori* selection of endpoints, and large sample size. Low-incidence cohorts are preferred for assessing how background, such as comorbidities, relates to risk of an adverse event. Identification of an independent drug-effect requires collection of other factors that may influence risk of developing the co-morbidity. Studies should be performed in regions with centralized and subsidized healthcare, or in a network setting with sufficient funds to ensure good follow-up. To minimize treatment bias, results should be blinded until a sufficient number of endpoints have accrued for reliable comparison. Data collection should not cease until study results are readily clearly apparent. Also, data collection should address causes of drug switch or drug discontinuation.

Cohorts may be combined to optimize study power. For this approach, there is a need to identify how to maximize data yield without compromising data quality. To this end, data collection should be focused and open-ended questions are strongly discouraged. On the other hand, a data collection scheme should allow for collecting data on interesting aspects that may emerge while a study is ongoing. Otherwise, unsuspected findings will not be studied and may not be detected. A uniformity and harmonization of data to be collected needs to be developed, as well as a means for merging databases. Inter-cohort collaborations should address questions that can only be answered by a sample size larger than the size of each individual cohort, since cohorts compete for science and funding.

An example of a cohort study that implements these concepts: the Data Collection on Adverse Events of anti-HIV Drugs (D:A:D) study, set up in 1999 to assess incidence of myocardial infarction with combination *antiretroviral therapy* (cART). The *a priori* hypothesis was that there would be a doubled incidence with more extended exposure to cART, requiring the collection of at least 100 cases of myocardial infarction. The study was completed in 2002, with 126 events.⁴⁸ The study was extended to determine the reproducibility of results and to assess specificity and mechanism of regimen-related myocardial infarction. It now includes 345 events and 7 years of follow-up. In the D:A:D study, there was an increased risk of myocardial infarction with exposure to protease inhibitors, but not with non-nucleoside reverse transcriptase

inhibitors. The increased risk with protease inhibitors was partially explained by lipid levels. Very few patients switched drugs or discontinued treatment due to cardiovascular disease.

In the prospective observational cohort study EuroSIDA (1994-2004), the risk of liver-related death at 1-year has over time declined by 7% per calendar year – a decline that was largely explained by improvement in immune function over the period. Risk was high in patients with hepatitis B or C virus.^{49 50} In the D:A:D study (2000-2004), liver failure and unknown infection with hepatitis B and C accounted for about 12% to 15% of deaths, which is similar to percentages of death due to cardiovascular disease. In both studies, the risk of liver-related death was gradually higher in patients with lower latest CD4+ count. Risk was not associated with HIV infection status (positive versus negative). With longer drug exposure to cART, there was a marginal increase in liver-related death, after adjusting for the latest CD4+ cell count. This signal of a possible gradually lesser benefit from cART after longer durations of exposure is currently being investigated further.

The D:A:D study examined over 23,000 patients from 11 existing cohorts yet still has insufficient power for assessing drug classes and individuals drugs on risk of liver-related deaths. However, class specific effects are of interest. How longer-term exposure to antiretroviral therapy affects risk of pancreatitis, renal function and malignancies under active investigation.

LONG-TERM SAFETY MONITORING:
THE ACTG LONGITUDINAL LINKED RANDOMIZED TRIALS (ALLRT) COHORT

The ACTG *Longitudinal Linked Randomized Trials* (ALLRT) Cohort is a prospectively planned series of meta-analyses and cross-protocol analyses of subjects enrolled in ACTG trials that provided randomized anti-retroviral therapy or immune-based treatment regimens to antiretroviral-naïve or -experienced patients. The primary objective of ALLRT was to evaluate long-term (5+ years) outcomes of potent combination antiretroviral therapy: virological, immunological, and pharmacologic/pharmacogenomic outcomes, clinical endpoints, adverse effects, quality of life, resource utilization, and neurological/cognitive effects. Data collection at entry was fairly comprehensive, and subjects are seen every 16 weeks. As of May 2006, 3,695 subjects were included. The mean follow-up from parent study entry is about 3.7 years for

antiretroviral therapy-naïve patients (maximum 8.9 years), and about 4.9 years for experienced patients (maximum 9 years). What follows is data as of March 15, 2006.

At baseline subjects were on average 38 years old, 8% current or prior injection drug users, 17% female, and 66% antiretroviral therapy-naïve. Median CD4+ cell count was 218 cell/ μ L, and about 16% of subjects had highly advanced disease (≤ 50 CD4+ cells/ μ L). The median virus load of HIV RNA 152,000 c/mL, and there was an even distribution of low and high virus loads. 50% of subjects are white, 23% black, 19% Hispanic and 8% other ethnicities and racial groupings.

From these subjects, close to 500,000 specimens of plasma, serum, viable peripheral blood mononuclear cells have been stored. Completed analyses include analyses of neurology, quality of life, 3-year treatment response, opportunistic infections endpoints, and influence of Hepatitis C Virus infection on lipid levels; manuscripts are in press or submitted for publication. Additional planned analyses include analyses of clinical events, treatment -related adverse events (including gender differences), durability of virologic response (viral load) and immunologic response (CD4+ cell count) after 4+ years of therapy, the influence of specific drug regimens and regimen type, genomic analyses, and participation in North American-ACCORD Database.

Opportunistic infections occurred among antiretroviral treatment-naïve individuals treated with potent combination antiretroviral therapy. Half of all opportunistic infections occurred more than 24 weeks after starting antiretroviral therapy. The incidence of parasitic infection was 3%, fungal infection about 40%, bacterial infection 10%, and viral infection 40%. There were 163 major opportunistic infections in 116 subjects (76% of subjects), most commonly with *Pneumocystis jiroveci* Pneumonia (20%) or esophageal candidiasis.

High pre-treatment viral load and low CD4+ cell count were associated with increased risk of opportunistic infection after starting antiretroviral therapy. Opportunistic infection was also associated with lack of increase in CD4+ cell count after starting antiretroviral therapy. Other risk factors included a history of opportunistic infection, and being female, which warrants further exploration. Evaluation of additional variables, including predictors of risk after 24 weeks, and interactions among variables, is underway.

The incidence of malignancy was 3% (10% major malignancy). However, this rate may be confounded by potential bias: in the ALLRT parent study, ACTG 5211, there were no cases of malignancy, and therefore by chance, ALLRT may have excluded patients who already had significant events.

The approach of ALLRT to examining long-term outcomes has several pitfalls. To avoid subject and investigator fatigue, the parameters that were followed were simplified. Over time, there was a loss of subjects in placebo control group, due to subject transition into therapy. Some AIDS clinical trials units would be excluded because they are not within reach of a CCR5 inhibitor trial site. Informed consent to being part of a long-term follow-up was long, and therefore subjects often consented after the initial visit. Finally, assessments in ALLRT are far more intensive than might be appropriate for long-term follow-up of large cohort.

SECOND SESSION: PANEL DISCUSSION AND PUBLIC RESPONSE

Following the series of presentations summarized above, three panels addressed specific questions posed by the FDA. Each panel included experts from academia, community/advocacy groups, pharmaceutical and diagnostic industry, and the regulatory agency.

MONITORING AND SAFETY

The following questions were presented to panelists and discussed by panelists and members of the audience:

6. The current proposal is to follow subjects who experience virologic failure for five years. Please discuss if all subjects, regardless of virologic success or failure should be followed for five years
7. Please provide recommendations for other potential adverse effects that require additional monitoring such as other bacterial and viral infections and malignancies.
8. What are the feasibility concerns for the five-year follow-up commitment?
9. What mechanisms can be used to ensure sufficient data collection and minimize loss to follow-up?
10. Please discuss design options to further establish the relationship between viral tropism and pathogenesis.

Panel Discussion

- Panelists agreed that all patients, not just those with virologic failure, need to be followed up long term.
 - The usefulness of long term follow-up of patients with virologic failure is reduced by the cross-over design (allowing participants to change from placebo to study drug following virologic failure) which diminishes the control group and generates bias due to differential length of follow up between those with virologic failure versus those with virologic success.
- The right length of follow-up time cannot be determined at this time.

- The success of such a program will depend on the composite of follow-up time, sample size and incidence rate of event.
- The analogy of the tenofovir program, demonstrating the long-term follow up needed for understanding long-term consequences may be useful in this setting.
- Clarity is needed on long-term follow-up of patients currently enrolled in trials versus long-term surveillance and monitoring of adverse outcomes.
 - What are the advantages of post marketing approval studies compared to following patients participating in the trials?
 - A jointly sponsored cohort including patients from the various sponsor's clinical development programs should be considered.
- Long-term follow-up data could be affected by concurrent participation of patients in trials of other investigational agents.
 - Long-term follow-up should be designed in a manner that doesn't negatively affect a patient's ability to participate in trials of other investigational agents.
- The issue of an appropriate control group remains to be resolved.
 - Bias in reporting events generated by the intense follow-up is an issue to be considered.
 - Cross-over and virologic failure decrease the placebo group over time.
- Potential immunologic consequences, including opportunistic infections, unusual infections and reduced tumor surveillance need to be considered.
 - Not known whether any direct immunologic effects will be observed, or whether any observed effects will be permanent or, conversely, whether the effect will be a temporary interference during the actual drug exposure. At present, there are no data or biologic basis to suggest a permanent effect.
 - All events (not just AIDS-defining) need to be collected.
- Cohort studies are useful for picking up major effects; they are not useful for picking up subtle effects.
- The potential impact of viral tropism changes is difficult to predict at this time as the implications for pathogenic consequences are not clear.

- Malignancies surveillance can be simplified given an appropriate control group, but experience in post-combination antiretroviral treatment era has demonstrated that the study of malignancy epidemiology is a moving target.
- The currently evolving clinical data will inform specific questions in order to be able to design the appropriate studies.
- Studies addressing the potential impact of tropism switch need to be well controlled, with specific and focused questions.
 - Patients exposed and not exposed should be followed over time, looking at tropism switch as a time dependent variable.
 - Better use of control arm in naïve studies needs to be considered.
 - Establish and follow a similar cohort on optimized background therapy without CCR5 antagonist exposure to look for consequences of tropism switch.

DISCUSSION OF RESISTANCE AND TROPISM ISSUES

The following questions were presented to panelists and discussed by panelists and members of the audience:

4. What degree of tropism change, for example, in an individual or in what proportion of subjects, would be cause for concern? Please consider this in both the presence and absence of effects on CD4+ cell count and viral load.
5. What resistance/tropism information is needed at the time of approval of new CCR5 co-receptor antagonists, and how much? Are data from a subset of study subjects acceptable, and if so, from what proportion?
6. What is the role of tropism/resistance testing in clinical practice (e.g. routine, optional, none?)

Panel Discussion: Significance of changes in viral tropism

- The field is now at a similar point with respect to viral tropism, changes in tropism and the potential clinical impact as it was at the time when the roles, contributions and impact of CD4 and viral load were being elucidated.
- The precise definition of switch is not clear: what is the threshold of clinical significance?
- It is clear that major switch issues have not been observed to date in clinical trials
- Frequently the X4 signal is very low (sub-threshold levels) yet real: does this have clinical significance?
- Tropism changes back and forth from R5 tropic to X4 tropic or mixed/dual tropic virus and vice-versa are frequently observed (in about 10% of patients) in the absence of CCR5 antagonist exposure, including in patients on combination antiretroviral therapy.
 - Any study designed to assess the role of tropism switch for pathogenesis will need to take this into account.
- Two questions need to be distinguished: the effect of tropism on CD4 cell count and viral load (or the pathogenesis related issues) and the issue of tropism switch as a mechanism of viral escape (or the drug resistance issue).
- Two scenarios should be distinguished:
 - enrichment of X4 tropic virus coincident with CCR5 antagonist exposure which is reversed upon discontinuation of the drug is probably of less concern than if the changes remain after discontinuation
 - any impact of X4 enrichment on viral load or CD4 cell count would affect the risk:benefit balance, and even a low incidence of such events would have an impact
 - if there is an effect on CD4 cell count, the slope of decline over time should be followed
- Although it is difficult to specifically advise the agency at this time, tropism switches in the absence of viral load or CD4 effects would likely not seem to be important.
- The causal nature of the relationship between X4 tropic virus and HIV pathogenesis is not clear:

- arguments to support both directions are available, but this question cannot be answered at this time
- it is possible that both directions are relevant
- it is possible that consequences will be different for naïve versus experienced patients

Panel Discussion: Diagnostic issues

- Confusion exists regarding what the currently used diagnostic assays demonstrate.
- Historically, more familiarity exists between the syncitium-inducing (SI) and non-syncitium-inducing (NSI) assay in the context of natural history studies, but this assay is no longer used.
 - SI and NSI implications for pathogenesis have not been studied in patients on treatment
- Currently, researchers are attempting to assess the clinical significance of “blips” of X4 tropic virus detection without natural history studies to provide context.
- Clarity is needed on whether it is an issue of *relative* increase or *absolute* increase in X4 tropic viruses:
 - a *relative* increase of X4 tropic virus would not be as significant (simply a matter of an increased chance of detection) as an *absolute* increase (indicating a potentially preferential expansion of this viral population)
 - In the available tropism assay, inhibition of R5 virus by a CCR5 antagonist would be expected to increase detection of X4 virus, even in the absence of any absolute increase in the amount of X4 virus

Panel Discussion: Drug resistance

- The FDA would like to know: why are people failing, what is the predominant reason for virologic failure? Reasons for failure include:
 - Outgrowth and/or switch (the consequence possibly would be no response to other drugs in this class) due to
 - undetected X4 tropic virus at baseline,

- actual switch (evolution to new tropism)
 - “Classic” drug resistance to antagonist
 - Resistance to other drugs in the regimen
- To answer these questions, appropriate data is required, including clonal analysis of viral populations at baseline
- The cost and resource intensive nature of the required studies need to be recognized
 - How many patients do we need to be able to answer these questions?
- Specific advice on the number of patients that need to be studied cannot be provided at this time, given our limited knowledge.
 - The envelope region of HIV is a complicated region, with great variability between patients
 - Viral clonal analyses are absolutely required in clinical trials
- The field will benefit if resistance related information, reagents and isolates are shared across companies and with collaborators

Panel Discussion: Use of assay

- In treatment naïve patients, a tropism diagnostic assay likely will be essential to identify suitable candidates for CCR5 antagonist treatment in order to minimize the risk to other drugs in the regiment, should the patient have X4 tropic viruses
- Monitoring at time of failure may be important if switch is associated with adverse outcome

CLINICAL EFFICACY STUDY DESIGN & PEDIATRIC ISSUES

The following questions were presented to panelists and discussed by panelists and members of the audience:

3. How will the CCR5 antagonists fit into the antiretroviral armamentarium?
4. Given the issues previously discussed are there any special/additional concerns for pediatric drug development?

Panel Discussion: CCR5 in antiretroviral armamentarium

- In cases where active agents are available from multiple treatment classes, safety is the most important feature determining what agents are used.
- Combining compounds within the drug-class and with drugs in other classes is of great interest.
- The greatest need for new classes of drugs, with new mechanisms of action, is in treatment-experienced patients who have resistance to currently available drugs.
 - In advanced disease, up to 50 percent of patients have dual/mixed virus, which negatively impacts the virologic activity of CCR5 antagonists, underscoring the potential need for tropism testing.
- In treatment-naïve patients, currently available regimens present a higher barrier to a new class of drugs:
 - Current regimens are efficacious, convenient, safe, and with manageable drug-drug interactions in most patients, but there remains room for improvement
 - The fact that 80% to 90% of treatment-naïve patients have CCR5-tropic virus makes CCR5 antagonists an appealing potential treatment option.
 - CCR5 inhibitors, if safe, may serve niche populations:
 - women of child-bearing potential
 - people with non-nucleoside reverse transcriptase inhibitor resistant virus
 - patients who are intolerant to side effects of non-nucleoside reverse transcriptase inhibitors
- CCR5 antagonists may also play a role in treating acute infection, in pre- and post-exposure prophylaxis, and as active components in microbicides.

Panel Discussion: Pediatric Issues

- Novel agents approved for use in adults, are anticipated to be widely used in children.
- The number of babies and younger children with HIV (in the developed world) is low and is anticipated to decrease due to routine testing for HIV during pregnancy.

- Most pediatric patients with AIDS are pre-teens, many of them have moved through sequential therapies, including multiple combination antiretroviral regimens.
- Some children have had to withdraw from some treatments due to toxicities.
- Some pediatric patients have fully controlled HIV replication with treatment, while others have highly resistant HIV.
- Pre-teens and teenagers with multi-drug resistant virus have a compelling need for a new drug-class
- For a heavily treatment-experienced pediatric population with few treatment options and a fair amount of off-label drug use, the FDA would entertain various types of protocols, even prior to approval, including a written request for a sponsor to obtain pediatric exclusivity.
 - Once a drug is approved for adults, the Pediatric Research Equity Act would require pediatric studies.
 - Phase 2 trials in adults may provide adequate data for initiating pediatric phase 3 trials parallel with adult phase 3 trials. It was also suggested that in phase 2 trials in adults, exclusion criteria may be extended to include adolescents.
- Long-term follow-up in children, in trials and in general in clinical practice, is challenging, and for safety, requires the development of plans to manage entrance into adolescence and adulthood.
- Obtaining data on pharmacokinetics, toxicity, and activity of CCR5 antagonists in children, particularly adolescent and peri-adolescent children, is imperative.
- Planning for pediatric therapeutic trials should be started sooner rather than later:
 - Such planning would benefit from knowing the efficacy of CCR5 antagonists in patients with dual/mixed virus.
 - Short- and long-term toxicity and adverse events in pediatric patients is unknown currently.
- It would also be of interest to know:
 - the size of the pediatric population with drug-resistant HIV who would be candidates for CCR5 antagonists, as well as other drug-classes, and
 - what proportion of children have CCR5-tropic, CXCR4-tropic, or dual/mixed virus

- Immunologic response to a recall antigen in children receiving a CCR5 antagonist compared to a control group of children not receiving a CCR5 antagonist should be assessed:
 - Specifically, sustainability of titers should be compared.

APPENDIX A: AGENDA

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 <ul style="list-style-type: none"> ✓ 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 <ul style="list-style-type: none"> ✓ Current Requirements for Approval ✓ Proposed Monitoring plans ✓ Summary of Responses 	Scott Proestel
09:50 10:10	LONG-TERM SAFETY MONITORING <ul style="list-style-type: none"> ✓ ACTG experience ✓ Observational Cohort Experience 	Dan Kuritzkes Jens Lundgren
10:30-10:45	BREAK	
	SESSION II: PANEL DISCUSSION AND PUBLIC RESPONSE	Chairs: Roy Gulick & Joe Eron
10:45–12:30	PANEL A: MONITORING & SAFETY	Moderator: Roy Gulick
12:30 – 1:30	LUNCH	
1:30 – 3:00	PANEL B: VIRAL TROPISM & RESISTANCE	Moderator: Joe Eron
3:00-4:00	PANEL C: CLINICAL EFFICACY AND STRATEGY	Moderators: Roy Gulick and Joe Eron
4:00 – 4:15	WRAP-UP	

APPENDIX B: MODERATORS, PRESENTERS AND PANELISTS

Moderators & Presenters	
Debra Birnkrant, MD	Director, Division of Antiviral Drug Products, Center for Drug Evaluation & Research, FDA
Joe Eron, MD	Associate Professor of Medicine, University of North Carolina, Chapel Hill, NC
Roy (Trip) Gulick, MD, MPH	Associate Professor of Medicine, Weill Medical College, Cornell University, New York, NY; Director of Cornell HIV Clinical Trials Unit
Dan Kuritzkes, MD	Professor of Medicine; Director of AIDS Research, Brigham & Women's Hospital, Harvard Medical School, Cambridge MA
Jens Lundgren, MD, DMSc	Professor; Director of the Copenhagen HIV Program, Hvidovre University Hospital, Copenhagen, Denmark
Veronica Miller, PhD	Director, Forum for Collaborative HIV Research; Associate Research Professor, The George Washington University
Scott Proestel, MD	Medical Officer, Division of Antiviral Products, Center for Drug Evaluation & Research, FDA
Panel 1	
Thomas Gegeny, MS	Executive Director of The Center for AIDS Information and Advocacy, Houston Texas
David Haery	Chair of the European Community Advisory Board, European AIDS Treatment Group
Katherine Laessig, MD	Medical Team Leader, Division of Antiviral Products, FDA
Richard Little, MD, MPH	National Cancer Institute, NIH
Howard Mayer, MD	Executive Director, Department of Clinical Research, Pfizer, New London, Connecticut
Judith Millard, PhD	GlaxoSmithKline, Durham, North Carolina
William Olson, PhD	Vice President, Research and Development, Progenics Pharmaceuticals, Inc
Paul Skolnik, MD	Director, Center for HIV Care and Research, Boston University Medical Center
Kate Squires, MD	Professor of Medicine and Director of the Division of Infectious Diseases, Jefferson Medical College, Thomas Jefferson University
Robert Yarchoan, MD	Chief of HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, NIH
Panel 2	
Stephen Becker, MD	Director of Clinical Development, AnorMed Inc (currently

	at Koronis Pharmaceuticals)
Richard Colvin, MD, PhD	Clinical Assistant in Medicine, Massachusetts General Hospital; Instructor of Medicine, Harvard Medical School, Cambridge, MA
Lynda Dee	President, AIDS Action Baltimore, Baltimore, MA
Steve G. Deeks, MD	Associate Clinical Professor of Medicine, University of California San Francisco, San Francisco, CA
James F. Demarest, PhD	Senior Investigator, Clinical Virology, GlaxoSmithKline; Adjunct Assistant Professor, Department of Immunology, Duke University Medical Center, Raleigh-Durham, NC
Wayne Greaves, MD	Senior Director of Global Clinical Development, Schering-Plough Research Institute
John Moore, PhD	Professor of Microbiology & Immunology, Weill Medical College, Cornell University, New York, NY
Lisa Naeger, PhD	Division of Antiviral Drug Products, Center for Drug Evaluation & Research, FDA
Neil Parkin, PhD	Senior Scientific Director in Research and Development, Monogram Biosciences, San Francisco, CA
Jonathan Schapiro, MD	National Hemophilia Center, Israel; Adjunct Professor, Stanford University, Stanford, CA
Panel 3	
Panelists from panels 1 and 2	
Andy Wiznia, MD	Director of Adult and Pediatric HIV Services, North Bronx Healthcare Network; Professor of Pediatrics, Albert Einstein College of Medicine, New York, NY

APPENDIX C: CHEMOKINE ANTAGONIST WORKING GROUP STEERING COMMITTEE

Ben Cheng	Forum for Collaborative HIV Research
Wayne Greaves	Schering Plough Research Institute
Roy Gulick	Weill Medical College, Cornell University
Lynda Dee	AIDS Action Baltimore
Dan Kuritzkes	Harvard Medical School
William Freimuth	Human Genome Sciences
Howard Mayer	Pfizer
Judy Millard	GlaxoSmithKline
Veronica Miller	Forum for Collaborative HIV Research
Jeffrey Murray	FDA
Neil Parkin	Monogram Biosciences
Kimberly Struble	FDA

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- ⁴² Kaiser Permanente
- ⁴³ Gates, AmFAR, the International AIDS Society
- ⁴⁴ GlaxoSmithKline, Schering-Plough, Abbott Laboratories, AstraZeneca, Pfizer, and AnorMED Inc.
- ⁴⁵ NIH, CDC, and other government agencies.
- ⁴⁶ Abbott Laboratories, GlaxoSmith Kline, AstraZeneca, and Schering-Plough
- ⁴⁷ Abbott Laboratories, AIDS Treatment Action CoalitionBoehringer Ingelheim Pharm, Bristol-Myers Squibb, GlaxoSMithKline, Human Genome Sciences, InPhenoAG, Merck Research Laboratories, Monogram Biosciences, National Institutes of Health, Pfizer, Progenics Pharmaceuticals, Roche Pharmaceuticals, Schering Corporation, and Tibotec.

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