



**HIV FORUM**

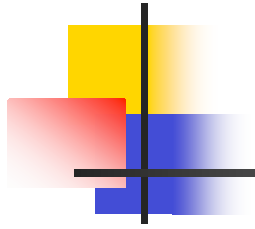
**23 May 2005**

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**CCR5 Inhibitors,  
A new class of entry inhibitors**

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# New pharmacological class

*More questions than answers...*

*Potential interaction with host*

*Deleterious impact on disease progression through the shift from R5 to X4*

*How to deal with the phenosense limitations ?*

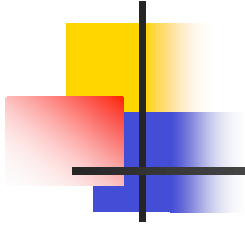
*How to deal with the link between the phenosense assay and the drug development (uncertainties on its (wide) availability at the time the drug will be registered) ?*



## Topic already discussed at the EMEA level

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- EMEA HIV Ad Hoc group : 8 Nov 2004
- Revised HIV guideline in circulation (limited amendments => *flexibility*)
- Comments expected until end of May 2005
- Up to now no scientific advice requested by applicants for CCR5 inhibitors



**SPECIFIC ISSUES IN THE DEVELOPMENT  
OF THESE NEW DRUGS :**



# PHARMACODYNAMIC SPECIFIC ISSUES

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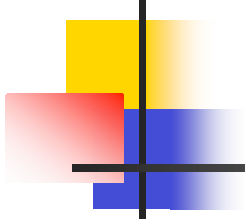
- **CCR5 specificity** (*versus other human chemokine receptors such as CCR2 or CCR4*)
- **R5 occupancy**



# PHASE II Studies

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- **Dose selection**
- **PK/PD relationship : R5 occupancy/viral load decrease**
- **PK parameter that correlates most with efficacy ?**



**Naïve patients with CD4 <200 :**  
*Unsuitable target for dose selection  
studies (Debate raised by EATG)*



## Naïve patients with CD4 <200 :

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### Potential ethical issue :

Dose selection study=> implies suboptimal dose (s) => potential deleterious impact through the switch from R5 to X4 **of unknown reversibility** => potential negative impact in the clinical evolution

*Whereas there is no unmet medical need*

*and*

*Whereas the initial treatment is of critical importance for the long term outcome of these patients*

*Is the inclusion of such patients compulsory in phase II studies ?*

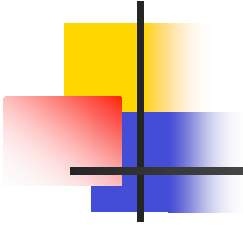




## *Scientific issue ?*

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- For any other drugs : reason to believe that the dose could be influenced by the sensibility of the viral strain => *potential interest to explore different doses for naïve and pretreated patients*
- For CCR5 inhibitors : reason to believe that the dose could be influenced by the R5 tropism whose indirect marker is the CD4 cell count=>*potential interest to explore different doses for patients with CD4 <OR >200/mm<sup>3</sup>*



*Is it compulsory to enroll such patients for dose selection (scientific issue?)*

*How to solve the ethical and scientific issues?*

*Topic for discussion...*



# Phase III studies

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- *Disputable* target Population
  - Antiretroviral experienced at advanced stage of the disease : *any benefit to be expected from CCR5 antagonists => Whitcomb and al. CROI 2003*



# Epidemiological data

*(Whitcomb and al. CROI 2003)*

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## ■ TORO 1

- BL RNA : 5.2 log<sub>10</sub> c/ml
- **BL CD4 : 80 cells/μl**
- Avg ARV drugs : 12
- ≥5 primary mutations ≈ 80%

## ■ TORO 2 (Europe)

- BL RNA : 5.1 log<sub>10</sub> c/ml
- **BL CD4 : 98 cells/μl**
- Avg ARV drugs : 12
- ≥5 primary mutations ≈ 90%

### Results were available for 612 baseline viruses :

Only 2% (n=12) of viruses were non-B clade

Viruses at baseline : **62 % (n=378) R5 tropic**, 4 % (n=23) X4 tropic,

34 % (n=211) dual tropic

***⇒ R5 tropic viruses were the most prevalent in this population of heavily pretreated patients***



# Inclusion/exclusion criteria

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- Inclusion
  - on the unique basis of VL and CD4
  - on CCR5 viral tropism/phenosense HIV assay
- Exclusion of CXCR4 and dual tropism
  - => Potential consequence in the extrapolation of the results*

*Importance of stratification criteria : CD4 (especially if not part of the inclusion criteria of phase III studies); T20...*



## *No need for specific primary endpoints*

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- Antiviral agent :
  - % of patients with undetectable viral load or VL decrease from baseline,  
*=> Surrogacy has been established => appropriate endpoints*

## DESIGNS TO BE CONSIDERED FOR PHASE III STUDIES

- ARV naïve

- Head to head comparison / Non inferiority versus an active comparator  
(*Ns/tTI??, NNRTI, PI*)

*(depends on the applicant's expectation on the CCR5 drug's future role in the multitherapy)*

- ARV pretreated

- Head to head comparison
- Superiority over placebo :
  - OB +X vs OB+pboX

*Classical approaches*



# Need to focus on specific issues

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- Criteria for virological failure to be clearly stated
  - In addition to the viral load criteria, how to deal with occurrence of shift R5=>X4 :
    - On an individual basis (double blind study)
    - As regards the stopping rules of the study : how to define the acceptable limit in term of increased rate of shift between both treatment arms?

⇒ *Critical importance of DSMB*

- Reversibility of the shift to be substantiated
- Any signal on immune toxicity (increase incidence of infections)





# FOLLOW-UP

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- No amendment as regards the currently recommended follow up for approval
  - For full approval :
    - in naïve patients : 48 weeks
    - In antiretroviral experienced patients : 48 weeks (*=>16 weeks for conditional approval*)
- Longer term follow-up to be planned :
  - Theoretical risk of immunotoxicity
    - No specific target for the follow-up but analysis of any increased risk of infection
  - X4 shift : clinical consequence, reversibility



# Phenosense HIV assay entry

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Two potential uses :

- To characterise the baseline tropism
- To identify the shift from R5 to X4

*Critical issues :*

- *limited performance (impact on the selected population, on the estimation of the shift)?*
- *uncertainties on its (wide) availability at the time the drug will be registered*



# Conclusions

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- Two potential risks associated with this new class :
  - Shift from R5 to X4 : with negative impact on disease progression
  - Deleterious impact on immune functions
- Importance of clear stopping rules to ensure a safe development
- Flexibility in the European guideline=> ultimately, balance between the benefit and the risk (*risk assessment to be adapted to the emergence of any signal on toxicity during the clinical development*)
- Limited amendments proposed on the current European HIV guidelines => awaiting for comments (end of May) ...and feedback from this meeting

<http://www.emea.eu.int/pdfs/human/ewp/063302en.pdf>