Emerging Issues in HIV Clinical Trials for new ARVs Roundtable

The Maraviroc Experience and the Future

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The Maraviroc Experience and the Future

Objectives

- To illustrate in the context of the maraviroc clinical development program how the landscape of HIV disease has changed

- Considerations on how HIV drug development could evolve to serve the needs of HIV infected patients within this changing landscape

HIV Landscape in 2004

- Large proportion of HIV infected patients were highly treatment experienced (TE) with multi drug resistant virus and needed >3 ARV drugs
  - Patients were viremic with no treatment options
  - Treatment Guidelines → Recommended goal → To decrease Viral Load (VL) in order to delay occurrence of Opportunistic Illnesses
  - VL suppression superseded safety and tolerability
  - Easy to enroll harder to treat patients in clinical studies
  - Treatment Experience was used as a means to enrich the clinical study population with patients harboring drug resistant virus
- Growing proportion started to switch therapy due to tolerability and convenience issues without experiencing virologic failure
- Large Treatment Naïve (TN) Population whose needs were not as urgent as the highly TE
- Maraviroc Clinical Development Program was designed within this 2004 landscape

Phase 3 Program in Patients with R5 HIV-1 Treatment-Experienced (TE)

	ARV-naïve	ARV-experienced	
Study	1026	1027	1028
Phase	2b→3	2b/3	2b/3
Design	MVC vs. EFV AZT/3TC (CBV)	OBT + PBO or MVC	
Randomization	1:1:1	2:2:1	2:2:1
Primary Endpoint	%<400/ <50 wk 48	Δ VL at wk 48	
Enrollment	721	601	475
Received Maraviroc	360	467	373

ARV – antiretroviral, EFV - efavirenz (Sustiva), VL - viral load, MVC – maraviroc, PBO - placebo
OBT - optimized background therapy, CBV – Combivir

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Learnings from the Maraviroc Development Program

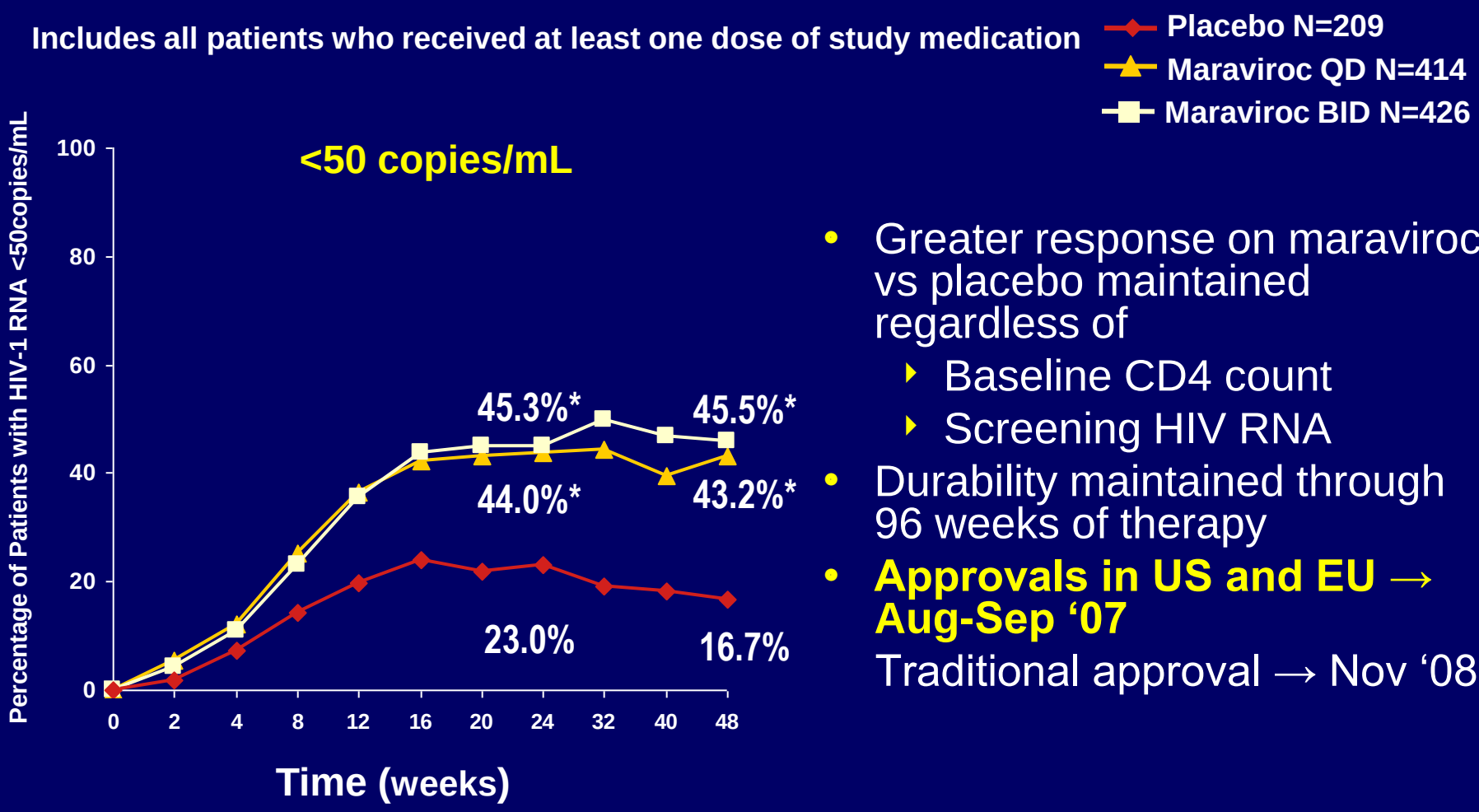
- In TE patients
  - Patients in placebo arm discontinued for lack of efficacy relatively early
    - Difficult to obtain meaningful comparative safety data
    - Delay in starting active open label drug may have potentially compromised all possible drugs to use in an OBT

- In TN patients
  - EMA guidance → Patients with low CD4+ T-cell counts included in exploratory studies only if scientific rationale and if data are available from patients with higher CD4+ T-cell counts
    - CD4+ entry criteria can then be relaxed in phase 3 studies
  - Studies in developing nations presents several challenges. Social and cultural issues need to be addressed for successful clinical study conduct
  - In Non-inferiority studies, still need to demonstrate a significant advantage over existing therapy

- Complexities of developing a drug-diagnostic assay pair

Maraviroc Regulatory Approval in TE patients

Includes all patients who received at least one dose of study medication



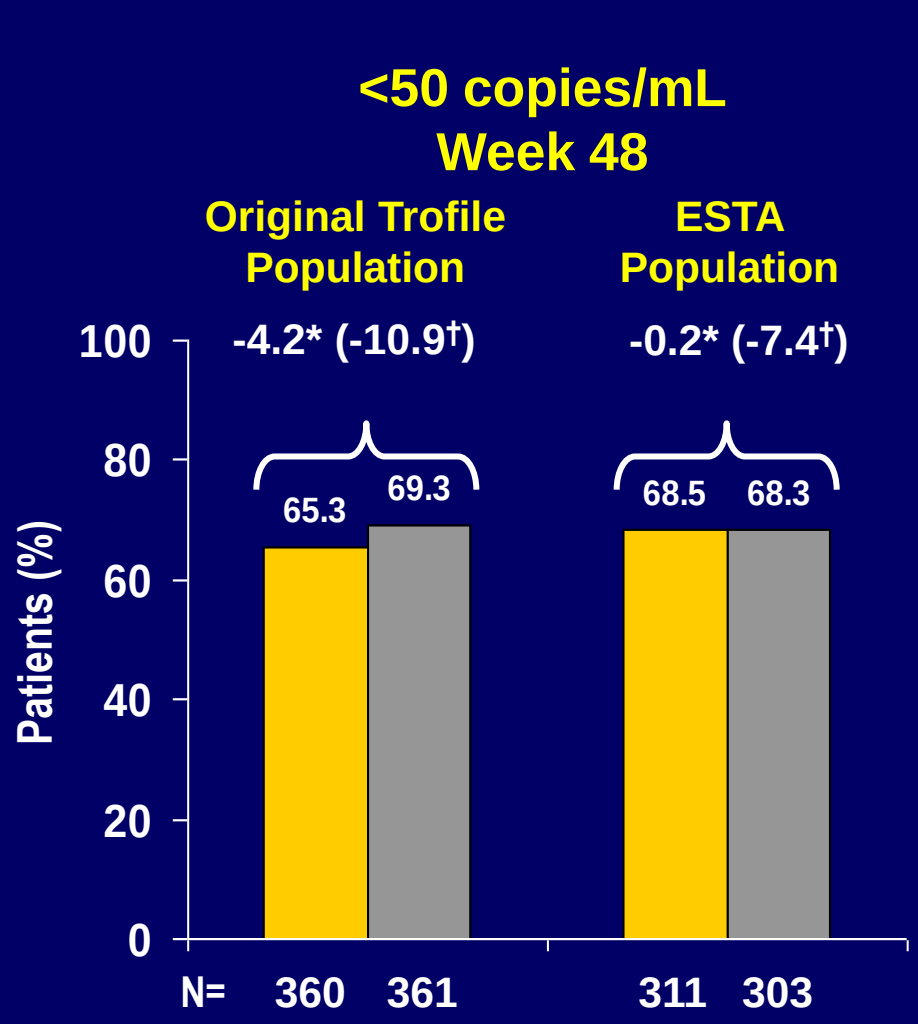
- Greater response on maraviroc vs placebo maintained regardless of
  - Baseline CD4 count
  - Screening HIV RNA
- Durability maintained through 96 weeks of therapy
- **Approvals in US and EU → Aug-Sep '07**

  Traditional approval → Nov '08

HIV-1 RNA value imputed as baseline if missing or if patient discontinued before 48 weeks
***p*<0.0001 vs placebo + OBT**

Hardy D, *et al. 15th CROI* 2008; Poster 792, Hardy D et al. 9th ICDTHI 2008; Poster O425
Gulick RM et al. NEJM 2008; 359:1429-41 Fätkenheuer G, et al. *NEJM.* 2008;359:1442-55

Maraviroc Regulatory Approval in TN patients



- Treatment differences fell within the Non-Inferiority Margin in the ESTA Population at Week 48
- US and Canada approvals → Nov ’09, Apr 2010
- EU considered application not approvable
- **Is demonstration of a positive risk benefit profile sufficient to offer prescribers alternative options or is an improvement over an existing risk benefit profile essential?**

***Difference (adjusted for randomization strata); †Lower bound of 1-sided 97.5% confidence interval**

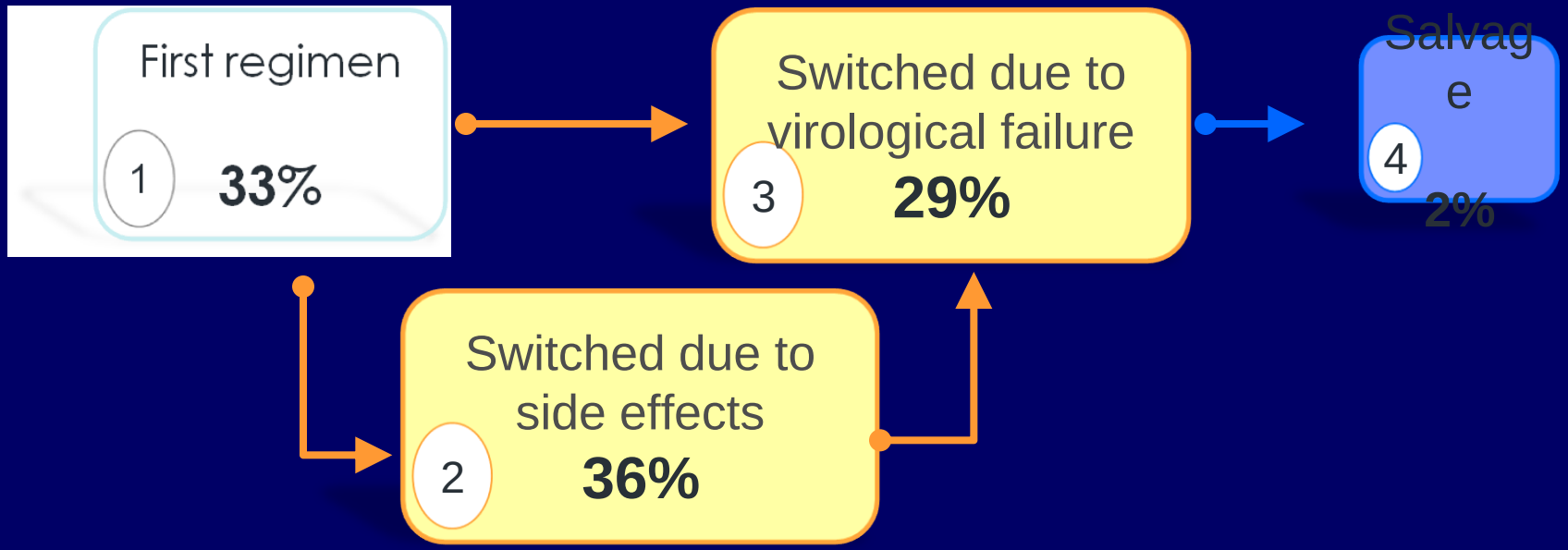
Includes patients who received at least one dose of study medication; missing values classified as failures

Key Post Marketing Commitments for Maraviroc

First host targeted HIV therapeutic and First in class

- 5 year long term follow-up of registrational studies (A4001026, 1027 and 1028)
- A4001067: 3000 patient safety registry (POEM)
  - Non-randomized, controlled, observational study to provide additional safety data on incidence of mortality, liver failure, malignancy, myocardial ischemia or infarction, rhabdomyolysis, and Category C infections
- A4001098: HCV and/or HBV co-infected patients
- A4001031: Pediatric study in 2 to 18 years of age
- Deferred pediatric study under PREA from birth to ≤ 2 years of age
- Development of a tropism diagnostic test
  - Submit application for a diagnostic test to FDA, on the part of a diagnostic sponsor(s) or as sponsor. Test to demonstrate performance adequate to identify an appropriate patient population for maraviroc use

HIV Landscape in 2013 and beyond



- Approximately 80% of patients across US and EU have undetectable VLs → very few patients available to recruit into TE studies
- Increasing life expectancy → Increasing duration on ARVs
- There will be multiple NRTI Fixed Dose Combinations (FDCs): Each patient may only benefit from one FDC
- There are multiple QD options
- There will be generic efavirenz
- Same safety and efficacy required from regimens regardless of Treatment experience

Morbidity and mortality causes in the virologically controlled patient and their relationship to inflammation

- Patients who have achieved long-term viral load control on HAART are now increasingly experiencing premature onset of diseases associated with aging, such as
  - cardiovascular (CV) disease
  - non-AIDS cancers
  - liver disease
  - renal disease
- These serious non-AIDS diseases are being observed at an excess rate compared to the general population
- These endpoints were initially not thought to be related to immune deficiency or HIV, however recent data suggests that persistent HIV-induced immune dysfunction is associated with this excess
- ARVs may also contribute to many of these endpoints
- Although there's a switch in paradigm to treating patients earlier, many patients do present with very advanced disease
  - These patients are more likely to experience these clinical endpoints

Engels EA. *AIDS* 2009; 23:875-885.

Needs of an HIV patient in 2013 and beyond

- Cure (elusive)
- Need for therapies that minimize residual inflammation and immune activation
  - To decrease non-HIV associated events
- Non-NRTI containing Fixed Dose Combinations
- Regimens that are safe and effective over the long term, convenient and well tolerated in ALL patients regardless of treatment experience
  - Trials should demonstrate this in patients whose virus is sensitive to all drugs in the regimen being tested regardless of treatment experience
- There are still patients with multi drug resistant virus in need of new therapies with novel mechanisms of action
  - We would predict that over time this need will not diminish as multi drug resistance is likely to increase as with most infectious diseases

Registrational Clinical Study Design Issues

- In TE studies that enroll patients with multi drug resistant virus, having a fully active background is necessary to achieve current goals of therapy
  - Potent activity of backbone decreases the ability to ascertain contribution of the investigational agent
    - DRV/r + RAL + [ETR or LRV]

- Resistance criteria in non-inferiority studies need to account for both test drug and comparator, further limiting patient pool, e.g.:
  - ETR – less activity against Y181C
  - LRV *in vitro* – active against Y181C

  Issue: Must exclude Y181C if ETR is used as a comparator

  Precludes ability to fully demonstrate LRV activity

- Are large scale pivotal studies in highly TE patients with multi drug resistant virus still feasible?

Phase 3 Proposal for an ARV being currently developed

Three Proposed studies for a drug with a new Mechanism of Action

1. **Pivotal: Virus is sensitive to all drugs (regardless of TE)**
   - OBT + Test Drug or SOC1
   - Eg. 2 sensitive NRTIs + Test Drug or EFV

2. **Pivotal: Virus is sensitive to all drugs (regardless of TE)**
   - OBT + Test Drug or SOC2
   - Eg. Boosted PIs + Test Drug or 2NRTI

3. **Supportive: Patients with Multi Drug Resistant Virus**
   - Open Label study to gather additional safety and PK information

- All studies would collect SMART endpoints, store samples for biomarkers and use scores combining organ functions (Justice)

Implications of the Evolving HIV Landscape for Drug Development

- Should labeling eliminate reference to Treatment Naïve vs Experienced populations?
  - Would sensitivity of virus to the drug and/or drug combination be more appropriate for including patients in studies and characterizing the drug in a label?
- Do we need to include a method of collecting endpoints (SMART type) that can be adjudicated?
- In addition to biomarkers, should scores combining different organ functions be included for the purpose of comparative effectiveness
- Post approval commitments
  - FDA –Prospective Observational Studies Safety Registry
  - Should long term safety of drugs and drug combinations be more appropriately assessed independently and driven by large cohorts supported by multiple pharmaceutical companies in a model similar to the HAART oversight committee rather than by individual companies?
  - Allows for larger databases to explore rare events, improves signal detection
    - Slow uptake of new drug
    - Inherent bias of cohort studies, but these also apply to safety registry