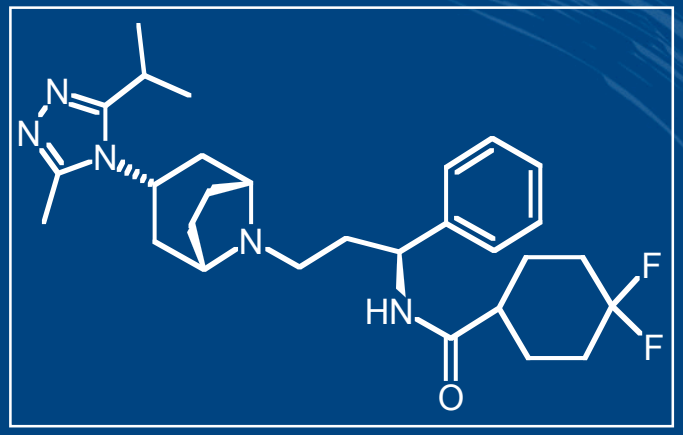
Maraviroc
A Case of Severe Hepatotoxicity

Targeting HIV Entry
1st International Workshop
2-3 Dec 2005
Bethesda, Maryland

Maraviroc (MVC, UK-427,857)

- Binds CCR5 (host cell target)
- Inhibits HIV entry of CCR5-tropic viruses
- Cross clade activity in vitro geo mean IC_{90}= 2 nM (1° isolates)

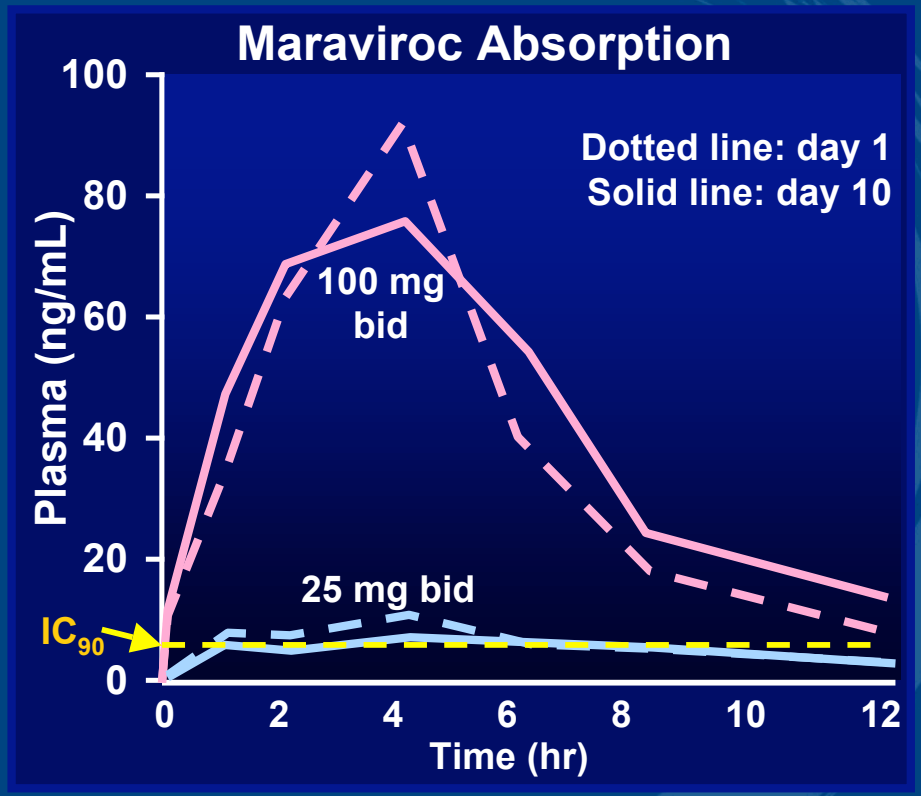


- Active against viruses with RTI/PI resistance mutations
- Additive-synergistic activity with existing antiretrovirals
- *In vitro* resistance is difficult to demonstrate

Dorr P *et al*. 10th CROI 2003. Abstract 12
Macartney MJ *et al*. 43rd ICAAC 2003. Abstract H-875
G Fätkenheuer *et al*.15th IAC 2004. Abstract TuPeB4489

Maraviroc Pharmacokinetics

- T_{max}: 0.5 to 4.0 hours
- Elimination half-life: 13 hours
- No accumulation over multiple dosing
- Metabolism primarily by cytochrome P450 3A4 and P-gp substrate
  - Does not induce or inhibit any of the P450 enzymes
- No clinically meaningful food effect
- Similar pharmacokinetics between
  - Healthy volunteers and patients
  - Males and females
  - Asians and Caucasians



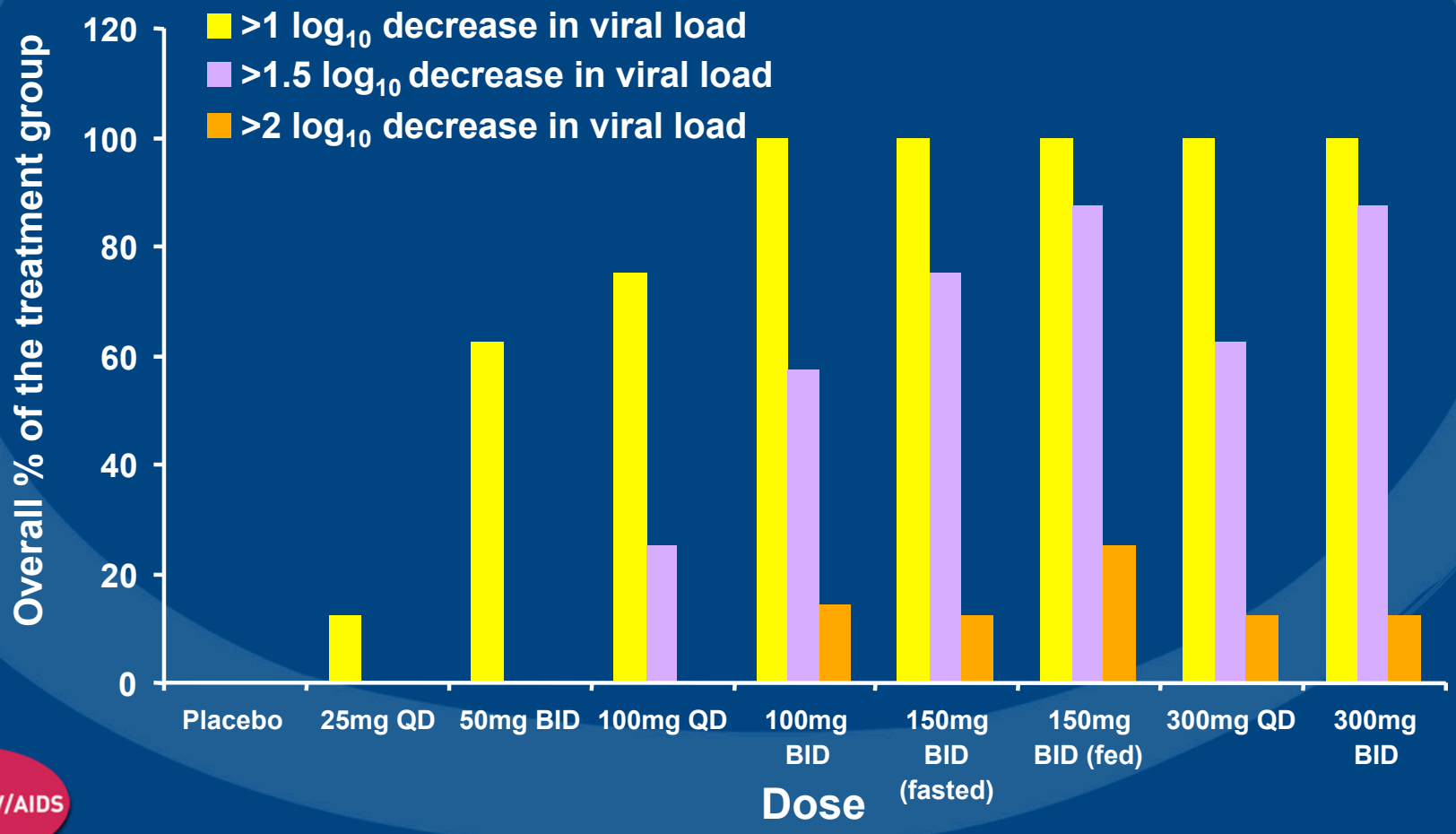
Abel S, et al. 43rd ICAAC. Washington, DC, 2004. Abstract 3066.
Abel S, et al. 5th WCPHIVT. Rome, 2004. Abstract 5.8.
Muirhead G, et al. 7th ICDTHIV. Glasgow, 2004. Abstract P283.
Jenkins T, et al. 5th WCPHIVT. Rome, 2004. Abstract 5.4.
Westby M, et al. 14th IDRW. Quebec City, 2005. Abstract 65.
Muirhead G, et al. 7th ICDTHIV. Glasgow, 2004. Abstract P282.

Maraviroc
Phase 1/2a Safety and Tolerability

	Volunteers	HIV Patients
Number of patients	>500	>65
Doses evaluated	Single doses: ≤1200 mg Multiple doses: ≤300 mg bid for up to 28 days	≤300 mg bid for 10 days
Serious AEs	None	None
Most common AEs	Headache, flatulence, dizziness, nausea	Asthenia, headache, dizziness
Clinically significant QTc prolongation	None	None

Maraviroc Monotherapy Data
Virologic response rates at nadir

- Mean maximum viral load reduction of ≥1.6log$_{10}$ at all doses of ≥100mg BID



Van der Ryst, et al. Viral Entry Workshop, Bethesda, MD, 2005.

Maraviroc Phase 2b/3 Program Overview

	A4001026	A4001027/8	A4001029
Population	ARV-Naïve R5	ARV-Exp'd, R5	ARV- Exp'd, Non-R5
Design	Phase 2b→3 **vs. EFV**	Phase 2b/3 **OBT add-on**	Phase 2b **OBT add-on**
1° Endpoint	% VL ND at wk 48/96	Δ VL at wk 24/48	Δ VL at wk 24
Sample size	1071	500/study	192

- More than 1,000 patients have been dosed with maraviroc
- More than 1,300 subjects have received multiple doses of maraviroc

ARV – Antiretroviral
EFV – Efavirenz (Sustiva)
OBT – Optimized Background Therapy
ND – Non-detectable
VL – Viral load

Pfizer HIV/AIDS

Maraviroc: DSMB Recommends Phase 2b/3 Studies Continue as Designed

- Maraviroc Independent Data Safety Monitoring Board planned meetings in July and September of 2005
  - Comprehensive review of maraviroc efficacy, safety, and laboratory data (including hepatic enzyme abnormalities)
  - Recommendation
    - All Phase 2b/3 clinical studies in antiretroviral-naive and antiretroviral-experienced patients for the investigational medicine continue as currently designed

Pfizer HIV/AIDS

Pfizer Press Release. Available at: http://www.natap.org/2005/HIV/101805_05.htm.

Aplaviroc

- September 2005[1]
  - Clinical trials in treatment-naïve patients terminated due to 2 cases of severe hepatotoxicity
    - Elevated AST/ALT and total bilirubin
- October 25, 2005[2]
  - HIV patient enrollment into Phase III treatment-experienced studies of aplaviroc were terminated due to liver toxicity concerns
    - 1 patient in one of the Phase III trials experienced elevated liver enzymes and total bilirubin
    - In the context of the previous reports from the Phase 2b studies, GSK has stopped all Phase III studies of aplaviroc
    - No further clinical studies of the compound are planned at this time

Pfizer HIV/AIDS

[1]GSK Press Release. Available at: http://www.gsk.com/media/pressreleases.htm.
[2]GSK Press Release. http://www.hivandhepatitis.com/recent/ad/102605_a.html.

Maraviroc
Patient with severe hepatotoxicity & rash

- Isolated case reported in early November 2005
- ARV-naïve patient in A4001026 unblinded and found to be receiving Maraviroc 300 mg once daily + Combivir
- This case different than those on aplaviroc
  - Sentinel and other aplaviroc hepatotoxicity cases occurred after long-term dosing[1]
  - Onset in this case after only 4 doses of maraviroc + zidovudine/lamivudine
  - In the setting of a diffuse erythematous rash
  - Multiple other confounding factors

Pfizer HIV/AIDS

[1]Nichols et al, EACS, Nov 19, 2005, Dublin, Ireland.

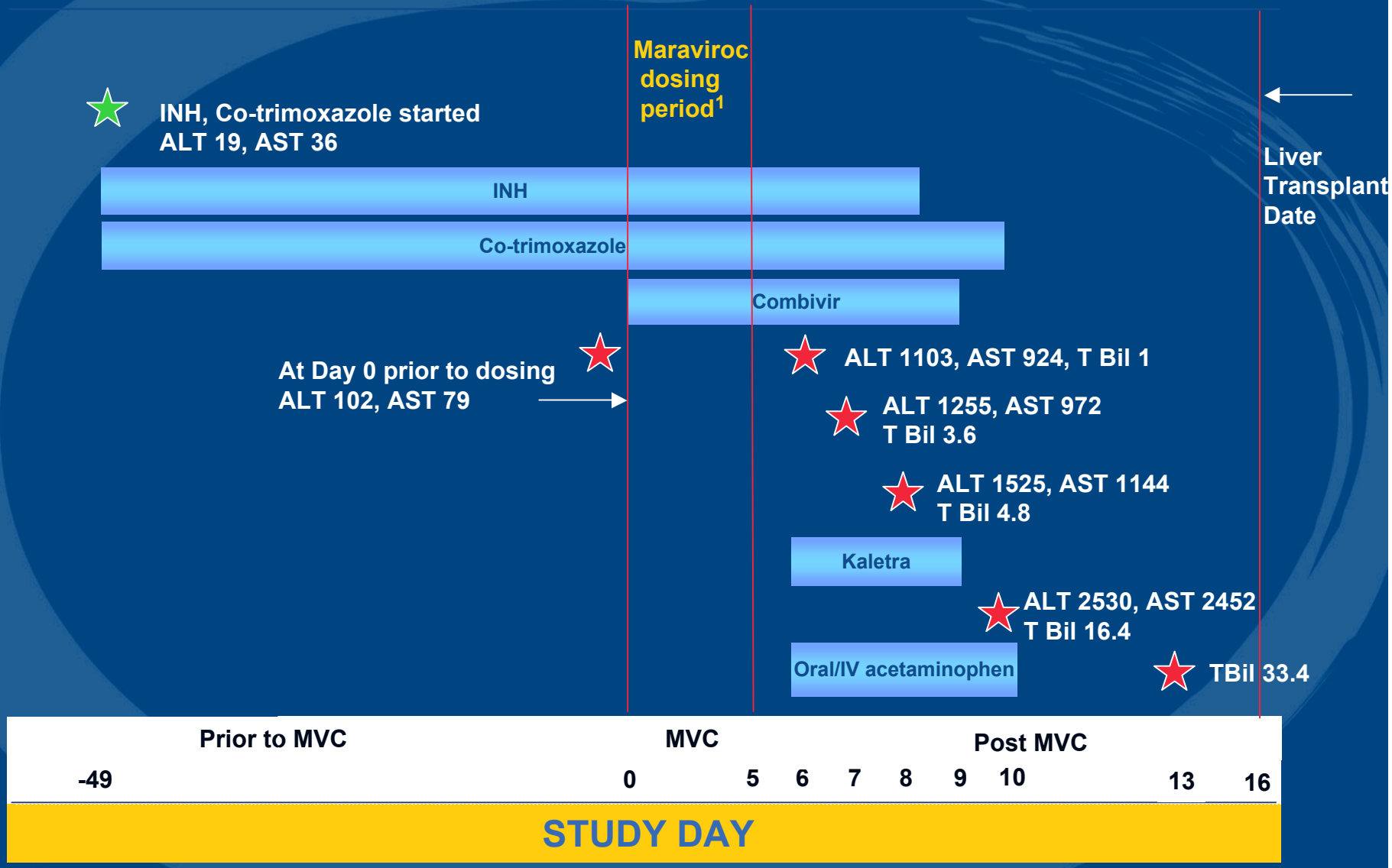
Patient with severe hepatotoxicity & rash Clinical Case Synopsis

- Radiographic evidence of underlying hepatic steatosis
- Seropositive for hepatitis C virus (HCV)
  - Undetectable HCV RNA
- Hypergammaglobulinemia, positive antinuclear antibody
- Seven weeks prior to dosing with maraviroc, isoniazid (INH) and co-trimoxazole (trimethoprim-sulfamethoxazole) were started for HIV-associated infection prophylaxis
- During this period, prior to maraviroc dosing, the patient's alanine aminotransferase (ALT) increased more than five-fold to 3 times the upper limit of normal (grade 2) with an elevated aspartate aminotransferase (AST)

Patient with severe hepatotoxicity & rash Clinical Case Synopsis *cont*

- After maraviroc was discontinued, and liver enzymes documented to be significantly elevated (ALT 32x ULN), potentially hepatotoxic medications were not discontinued
  - Isoniazid (INH)
  - Co-trimoxazole (Trimethoprim-Sulfamethoxazole)
  - Zidovudine/Lamivudine (Combivir)
- Other potentially hepatotoxic medications were initiated
  - Parenteral acetominophen (paracetamol)
  - Lopinavir/Ritonavir (Kaletra)
- The patient's liver enzymes worsened and these continued to decline, along with hepatic synthetic function, resulting in the need for urgent liver transplantation

Hepatotoxicity Case Timeline



[1]Patient received a total of 5 doses of maraviroc (1500 mg).

Steps taken to date

- Updated informed consent form for all new and existing patients to ensure that all patients are informed
- Investigators and regulators informed by comprehensive case summary
- Hepatologist and hepatopathologist consulted, await final report and other additional data on this case
  - Preliminary hepatologist assessment – consistent with severe drug induced hepatocellular injury; INH, co-trimoxazole or the study drug may be involved either singularly or in combination
- Ad-hoc DSMB meeting held on Nov 21st to specifically review this case and issue a formal clinical assessment and recommendations

DSMB Assessment and Recommendations

- The DSMB cannot exclude that maraviroc had some role in this patients illness. However the other medications administered during this episode appear to be more likely associated
- No changes to the program overall prior to the planned DSMB review in January
- Routine liver enzymes should be added to the randomization visit in all studies
- For ARV-naïve patients (A4001026), if a patient develops a Grade 3 or 4 abnormality in AST, ALT or total bilirubin, study drug and all potentially hepatotoxic medications should be discontinued immediately
  - Further management to be determined on a case by case basis

DSMB Recommendations *cont*

- Current or planned use of INH should be specifically added as an exclusion criterion in all studies
  - Patients who are currently receiving INH may continue
  - The use of INH during the study may be allowed on a case-by-case basis in consultation with the medical monitor
- The use of tipranavir/ritonavir should not be permitted as part of OBT in ARV-experienced patients (A4001027/8)
  - Until either more information is available on this case that clarifies causality or until more safety data on maraviroc are available
  - Patients who are currently receiving tipranavir/ritonavir as part of optimized background therapy (OBT) may continue
- Some of these recommendations will be reassessed at the planned January 2006 DSMB meeting

QUESTIONS?