Clinical Development Program and Clinical Trial Efficacy Results

Howard Mayer, MD
Pfizer Global Research & Development

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Overview

- Overview of the maraviroc Phase 2b/3 development program
- Clinical results in treatment-experienced patients with R5-tropic HIV-1
- Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1

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Maraviroc
Phase 2b/3 Program

	ARV-naïve	ARV-experienced		
	R5 Patients	R5 Patients		Non R5 Patients
Study	1026	1027	1028	1029
Phase	2b→3	2b/3	2b/3	2b
Design	MVC vs. EFV +CBV	OBT add-on		
Randomization	1:1:1	2:2:1	2:2:1	1:1:1
Primary endpoint	%<400/<50 wk 48/96	Δ VL at wk 24/48		
Enrollment	917	601	475	190
Received maraviroc		467	373	124

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

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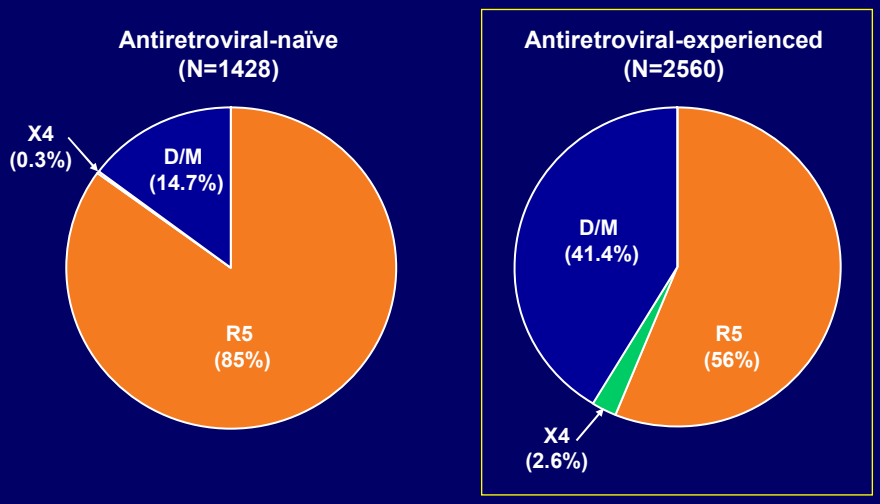
HIV-1 Tropism at Screening
Maraviroc Phase 2b/3 Program



Coakley et al. 2nd Int Workshop Targeting HIV Entry, October 2006

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Maraviroc Dosing Strategy
300 mg Dose Equivalent – QD and BID

Concomitant Antiretrovirals	Maraviroc Unit Dose
≥1 PI (excluding tipranavir/ritonavir) and/or delavirdine (± efavirenz)	150 mg *
All other regimens (including tipranavir/ritonavir)	300 mg

* Dose adjustment based on not significantly exceeding a 300 mg equivalent C_{max}

Muirhead G et al. *7th Int Cong Drug Ther HIV* 2004, abstract P283. Abel S et al. *5th Int Wkshp Clin Pharm HIV Ther* 2004, poster 5.8; Abel S, et al. 7th Int Wkshp on Clin Pharm HIV Ther 2006; Jenkins T et al. *5th Int Wkshp Clin Pharm HIV Ther* 2004, abstract 5.4; Muirhead G et al. *7th Int Cong Drug Ther HIV* 2004, abstract P282.

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Overview

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- Clinical results in treatment-experienced patients with R5-tropic HIV-1
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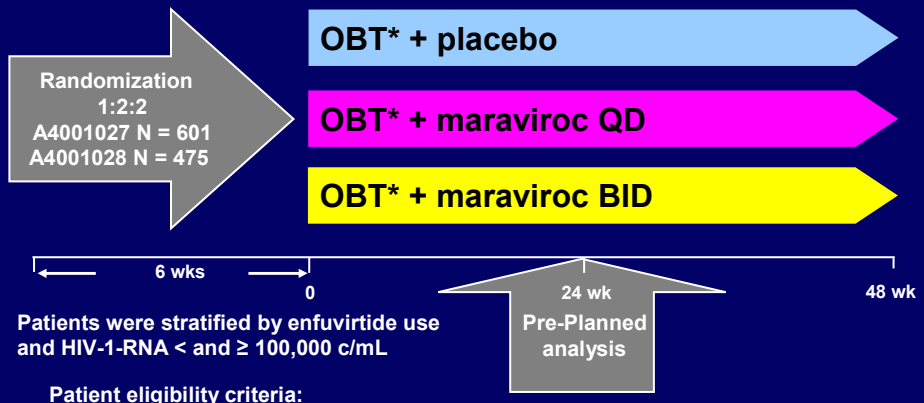
Trial Design
A4001027 and A4001028



Patients were stratified by enfuvirtide use and HIV-1-RNA < and ≥ 100,000 c/mL

Patient eligibility criteria:
- R5 HIV-1 infection
- HIV-1-RNA ≥ 5,000 c/mL
- Stable pre-study ARV regimen, or no ARVs for ≥ 4 weeks
- Resistance to and/or ≥ 6 months experience with ≥ one ARV from three classes (≥ two for PIs)

* OBT = 3–6 ARVs

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Primary and Secondary Endpoints
A4001027 and A4001028

- Primary Efficacy Endpoint
  - Change from baseline in $\log_{10}$ transformed HIV-1 RNA levels
  - Discontinuation = no change from baseline
- Key Secondary Endpoints
  - Percentage of subjects with HIV-1 RNA < 400 c/mL
  - Percentage of subjects with HIV-1 RNA < 50 c/mL
  - Change from baseline in CD4+ cell count*

* LOCF = Last Observation Carried Forward

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A4001027: Results

US, Canada

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Demographics and Baseline Characteristics

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

Randomized N = 601 Treated N = 585	Placebo + OBT N=118	MVC QD + OBT N=232	MVC BID + OBT N=235
Mean age, yrs (range)	46 (31–71)	46 (19–75)	46 (25–69)
Male, n (%)	106 (90)	210 (91)	212 (90)
White, n (%)	99 (84)	187 (81)	197 (84)
Median CD4 count*, cells/mm^3 (range)	163 (1–675)	168 (1–812)	150 (2–678)
Mean HIV-1 RNA*, $\log_{10}$ c/mL (range)	4.84 (3.46–6.02)	4.85 (3.20–6.75)	4.86 (3.26–6.88)
Enfuvirtide in OBT, %	42	43	46
≤ 2 active drugs in OBT (OSS), %	66	69	76

* Baseline for each patient calculated as the mean of up to three pre-dose assessments. (screening, randomization, and baseline visit)

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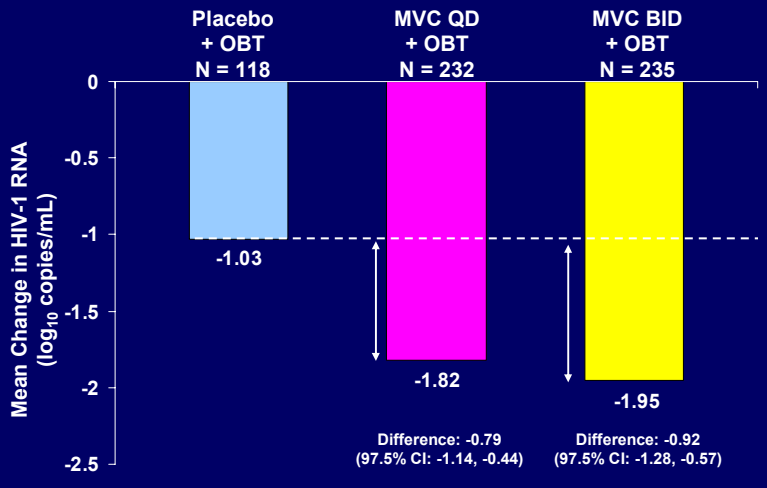
Mean Change in HIV-1 RNA from Baseline at Week 24

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



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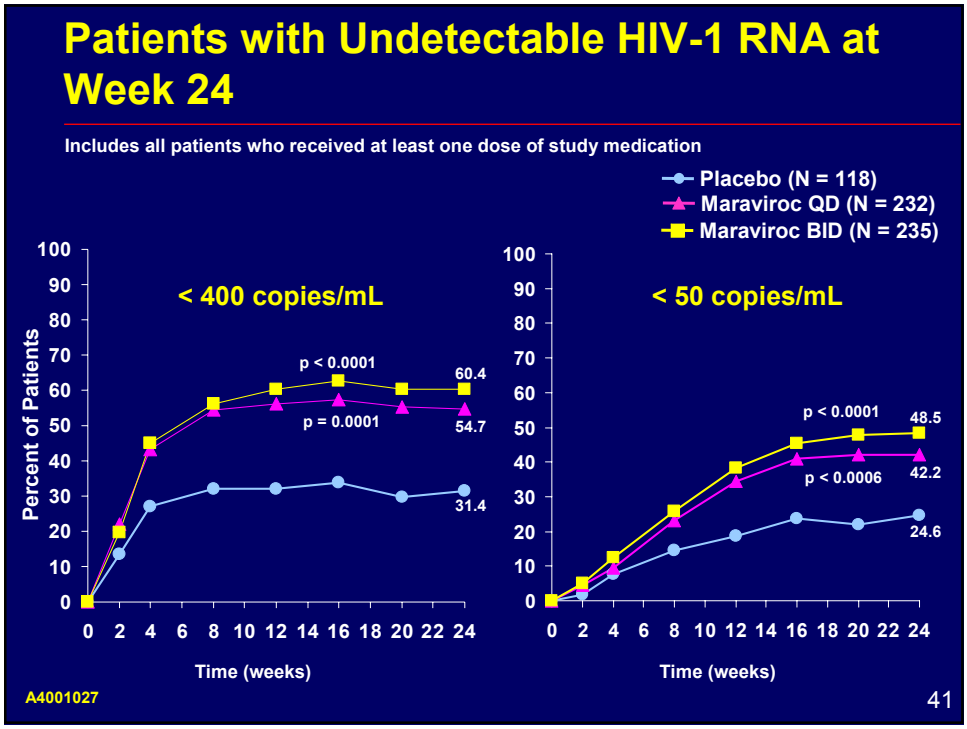
Patients with Undetectable HIV-1 RNA at Week 24
Includes all patients who received at least one dose of study medication
Placebo (N = 118)
Maraviroc QD (N = 232)
Maraviroc BID (N = 235)
< 400 copies/mL
< 50 copies/mL
Percent of Patients
Time (weeks)
p < 0.0001
p = 0.0001
p < 0.0001
p < 0.0006
60.4
54.7
31.4
48.5
42.2
24.6
A4001027
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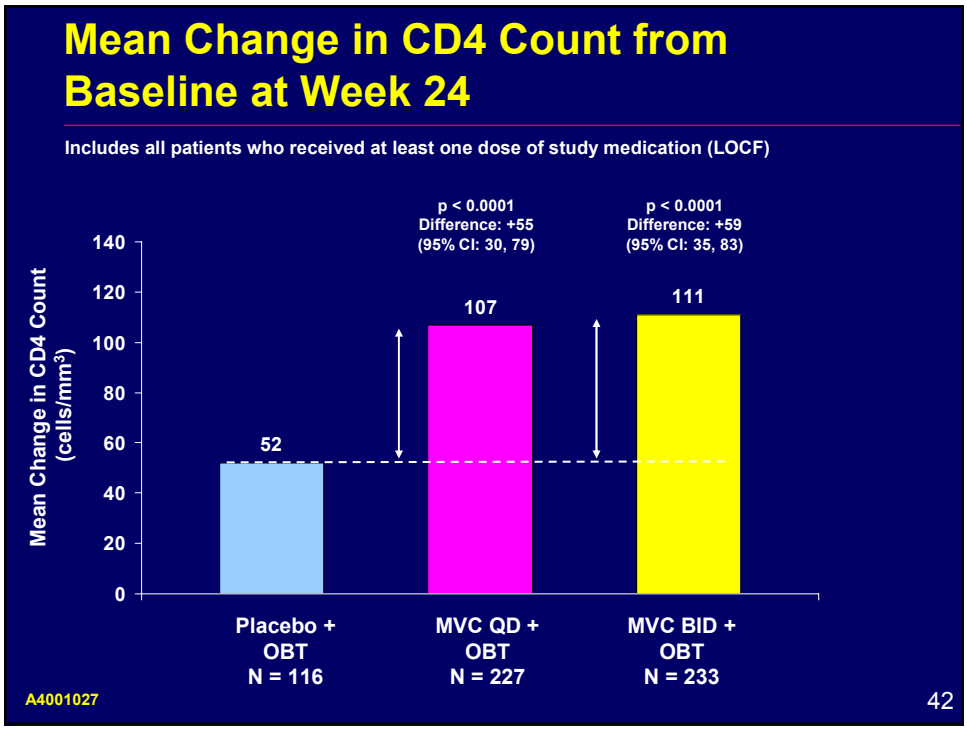
Mean Change in CD4 Count from Baseline at Week 24
Includes all patients who received at least one dose of study medication (LOCF)
p < 0.0001
Difference: +55
(95% CI: 30, 79)
p < 0.0001
Difference: +59
(95% CI: 35, 83)
Mean Change in CD4 Count (cells/mm3)
52
107
111
Placebo + OBT N = 116
MVC QD + OBT N = 227
MVC BID + OBT N = 233
A4001027
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A4001028: Results

Europe, Australia and US

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Demographics and Baseline Characteristics

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

Randomized N = 475 Treated N = 464	Placebo + OBT N=91	MVC QD + OBT N=182	MVC BID + OBT N=191
Mean age, yrs (range)	45 (29–72)	45 (17–75)	47 (21–73)
Male, n (%)	79 (87)	153 (84)	170 (89)
White, n (%)	79 (87)	149 (82)	166 (87)
Median CD4 count*, cells/mm^3 (range)	174 (2–545)	174 (1–966)	182 (3–820)
Mean HIV-1 RNA*, $\log_{10}$ c/mL (range)	4.89 (3.75–7.07)	4.87 (2.49–6.33)	4.84 (2.96–6.22)
Enfuvirtide in OBT, %	45	37	39
≤ 2 active drugs in OBT (OSS), %	66	63	62

* Baseline for each patient calculated as the mean of up to three pre-dose assessments. (screening, randomization, and baseline visit)

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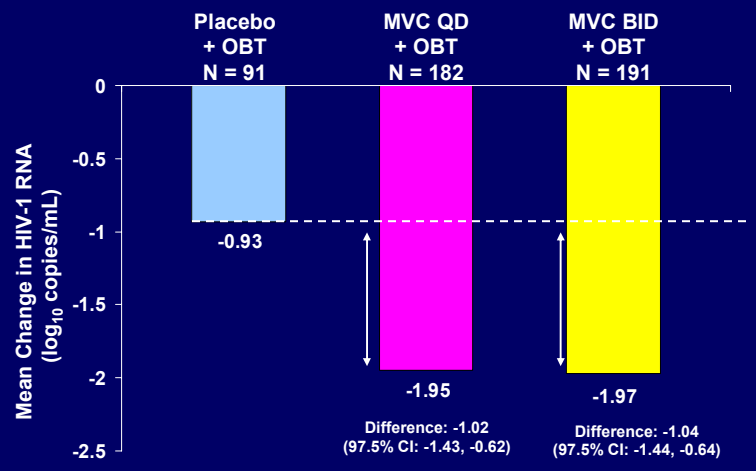
Mean Change in HIV-1 RNA from Baseline at Week 24

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



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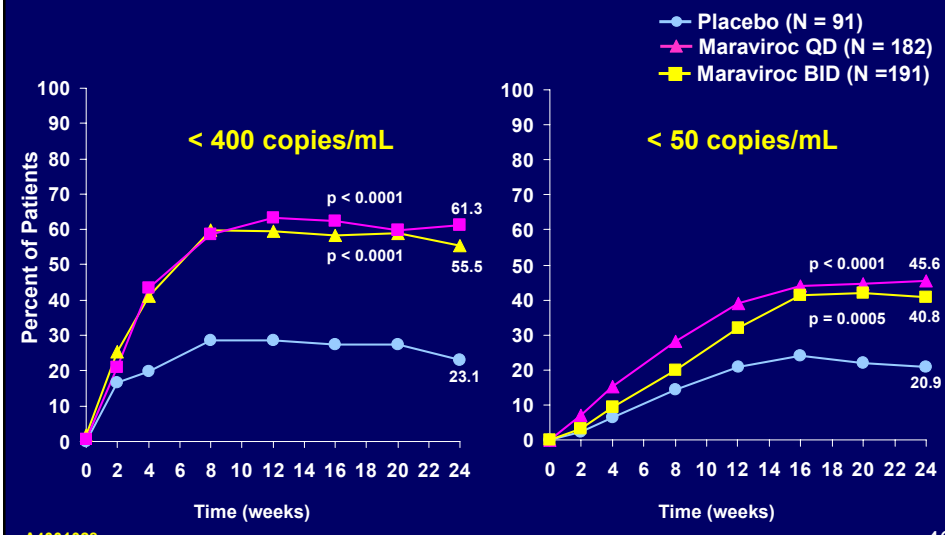
Patients with Undetectable HIV-1 RNA at Week 24

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



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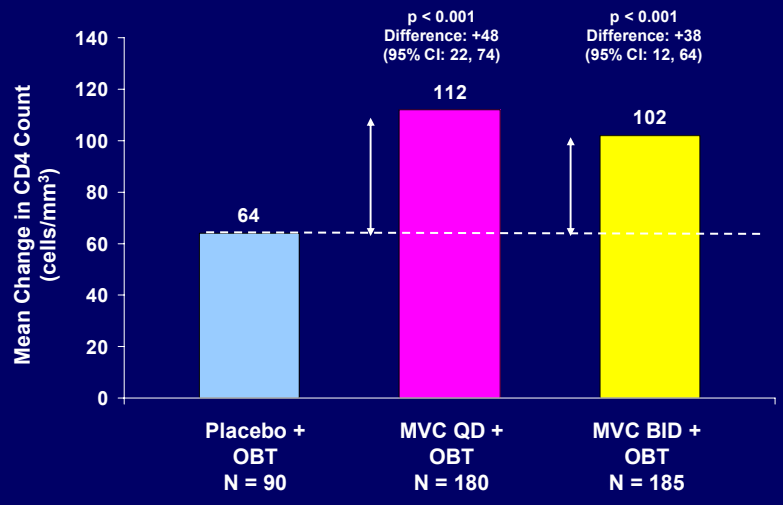
Mean Change in CD4 Count from Baseline at Week 24

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



A4001028

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Combined A4001027 and A4001028 Co-administered ARVs

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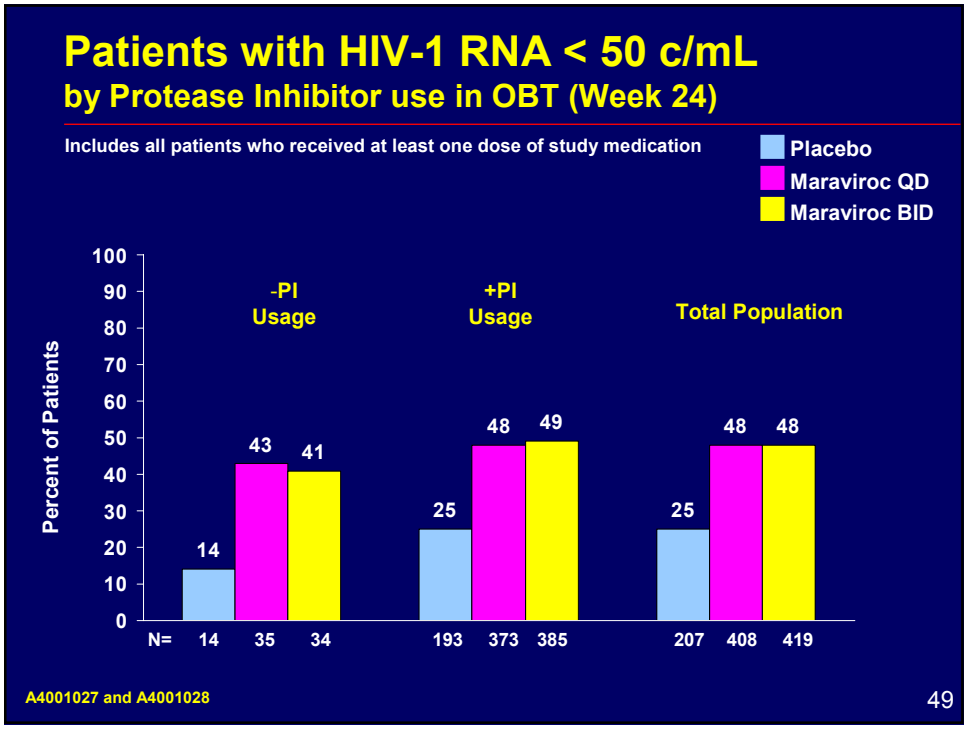
Patients with HIV-1 RNA < 50 c/mL
by Protease Inhibitor use in OBT (Week 24)
Includes all patients who received at least one dose of study medication
Placebo
Maraviroc QD
Maraviroc BID
Percent of Patients
100
90
80
70
60
50
40
30
20
10
0
-PI Usage
+PI Usage
Total Population
14
43
41
25
48
49
25
48
48
N= 14 35 34
193 373 385
207 408 419
A4001027 and A4001028
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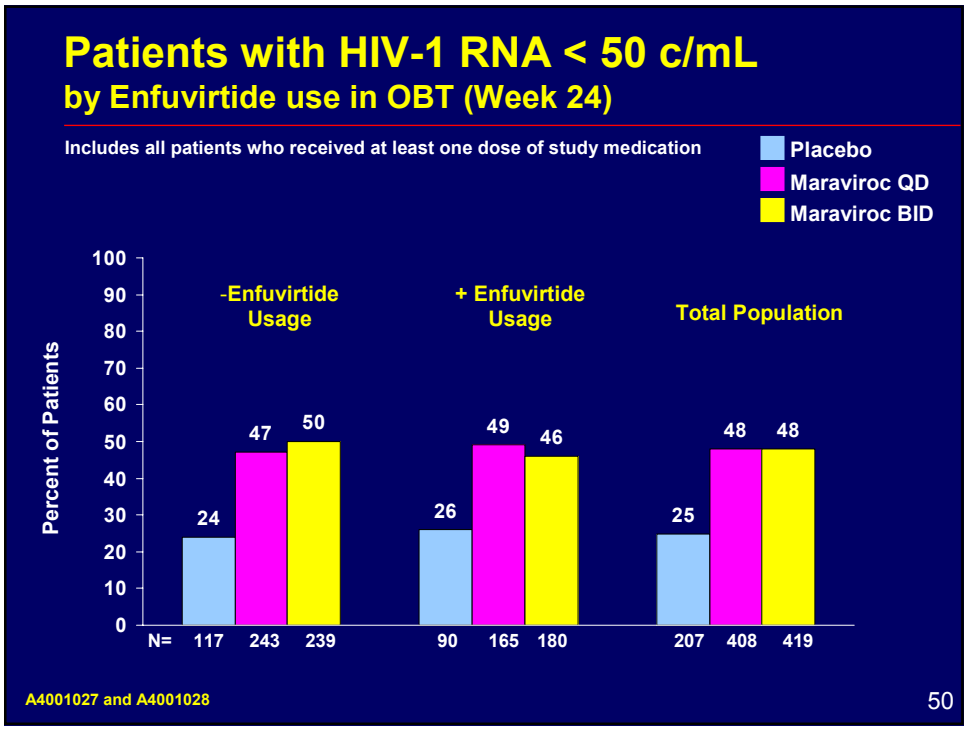
Patients with HIV-1 RNA < 50 c/mL
by Enfuvirtide use in OBT (Week 24)
Includes all patients who received at least one dose of study medication
Placebo
Maraviroc QD
Maraviroc BID
Percent of Patients
100
90
80
70
60
50
40
30
20
10
0
-Enfuvirtide Usage
+ Enfuvirtide Usage
Total Population
24
47
50
26
49
46
25
48
48
N= 117 243 239
90 165 180
207 408 419
A4001027 and A4001028
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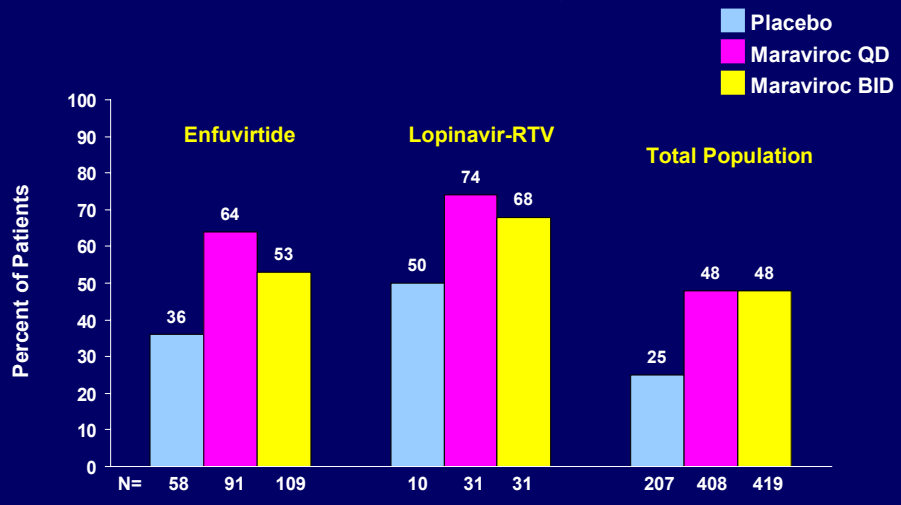
Patients with HIV-1 RNA < 50 c/mL
by Enfuvirtide/LPV-RTV First use in OBT (Week 24)

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



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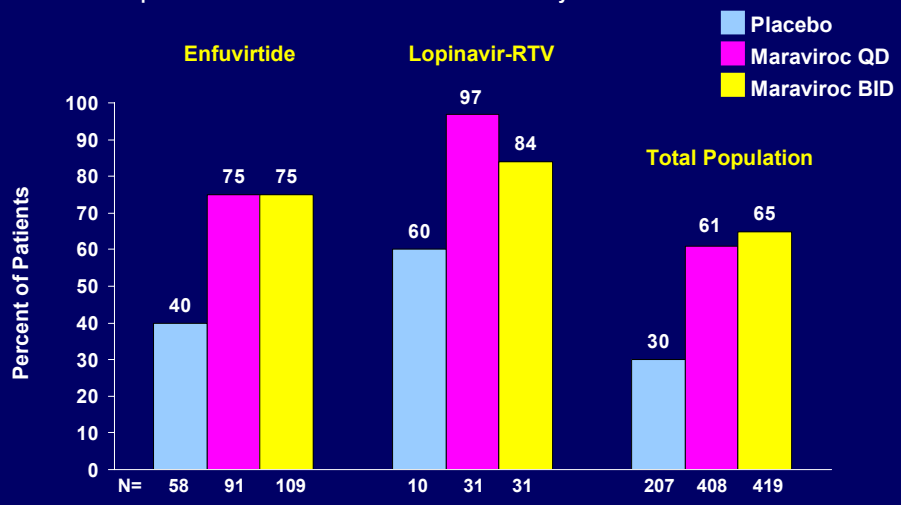
Patients with HIV-1 RNA < 400 c/mL
by Enfuvirtide/LPV-RTV First use in OBT (Week 24)

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



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Combined A4001027 and A4001028
Maraviroc QD vs BID

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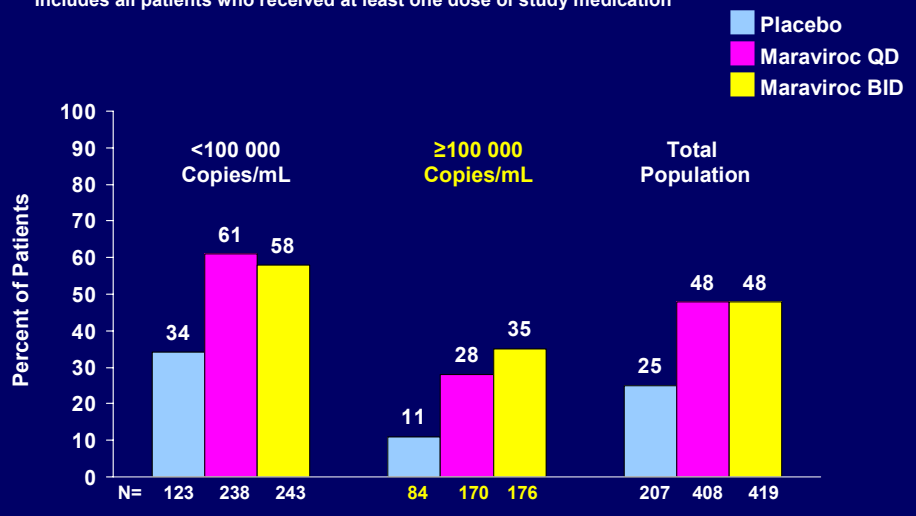
Patients with HIV-1 RNA < 50 c/mL
by Screening HIV-1 RNA (Week 24)

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



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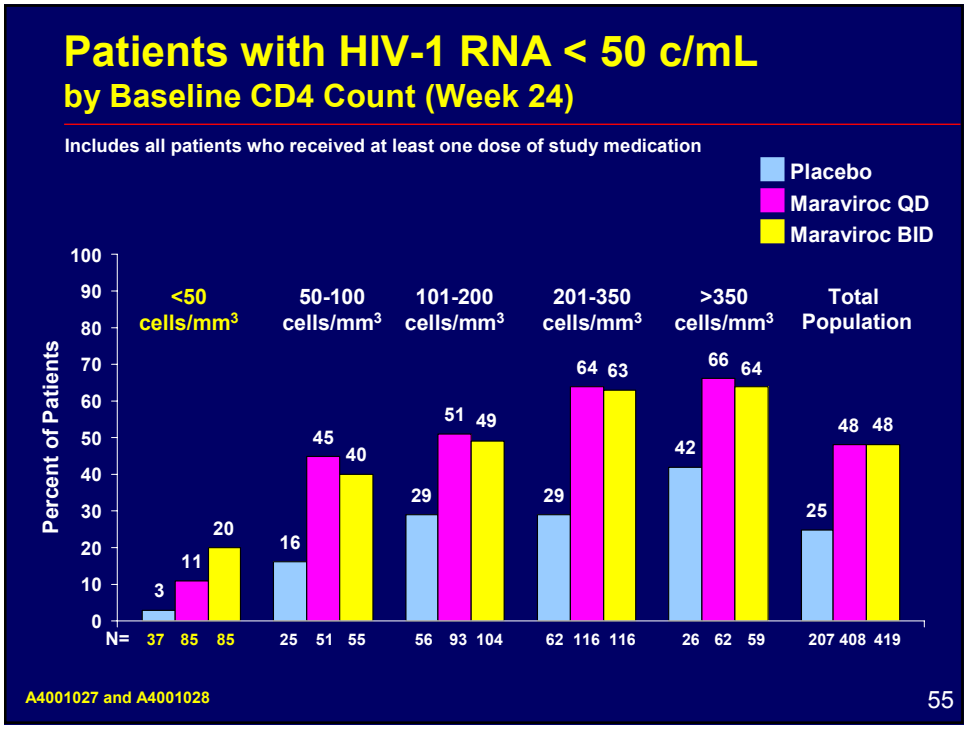
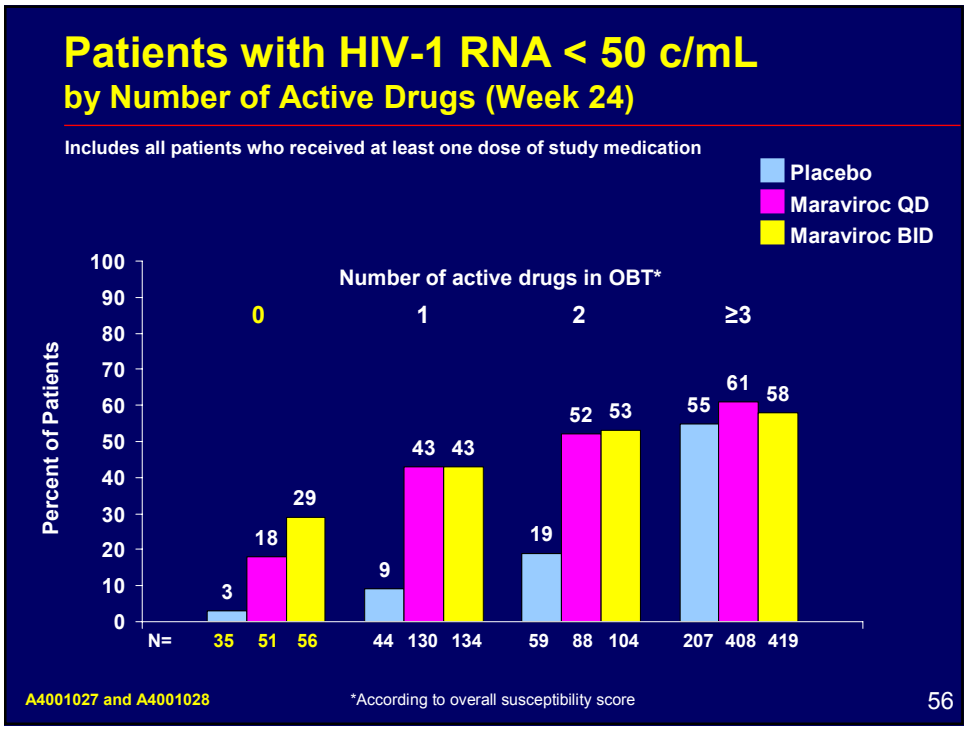

Patients with HIV-1 RNA < 50 c/mL
by Baseline CD4 Count (Week 24)
Includes all patients who received at least one dose of study medication
Placebo
Maraviroc QD
Maraviroc BID
Percent of Patients
<50 cells/mm3
50-100 cells/mm3
101-200 cells/mm3
201-350 cells/mm3
>350 cells/mm3
Total Population
3 11 20
16 45 40
29 51 49
29 64 63
42 66 64
25 48 48
N= 37 85 85
25 51 55
56 93 104
62 116 116
26 62 59
207 408 419
A4001027 and A4001028
55


Patients with HIV-1 RNA < 50 c/mL
by Number of Active Drugs (Week 24)
Includes all patients who received at least one dose of study medication
Placebo
Maraviroc QD
Maraviroc BID
Number of active drugs in OBT*
Percent of Patients
0
1
2
≥3
3 18 29
9 43 43
19 52 53
55 61 58
N= 35 51 56
44 130 134
59 88 104
207 408 419
A4001027 and A4001028
*According to overall susceptibility score
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Pharmacokinetic/ Pharmacodynamic Analysis Maraviroc QD vs BID

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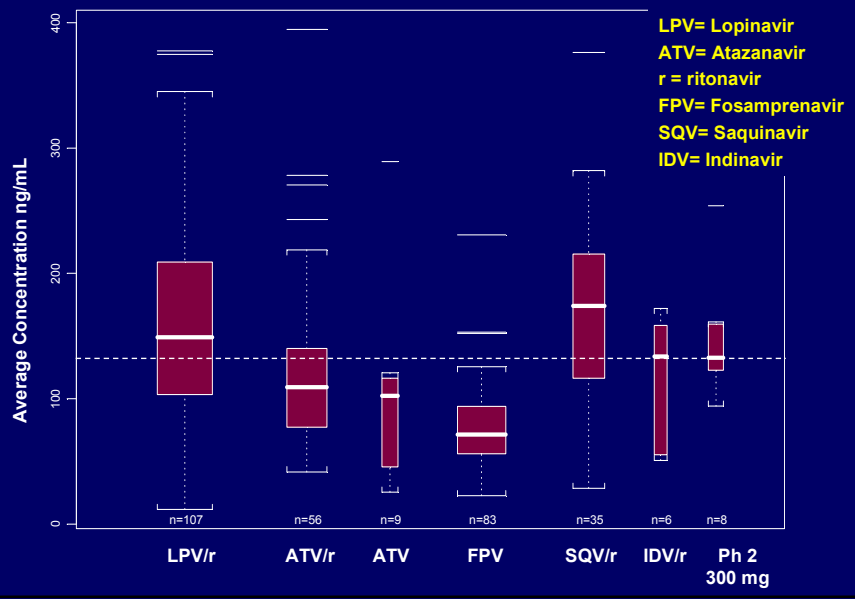
All ARV Experienced – 150 mg QD Group

Single PI vs. Phase 2a 300 mg BID



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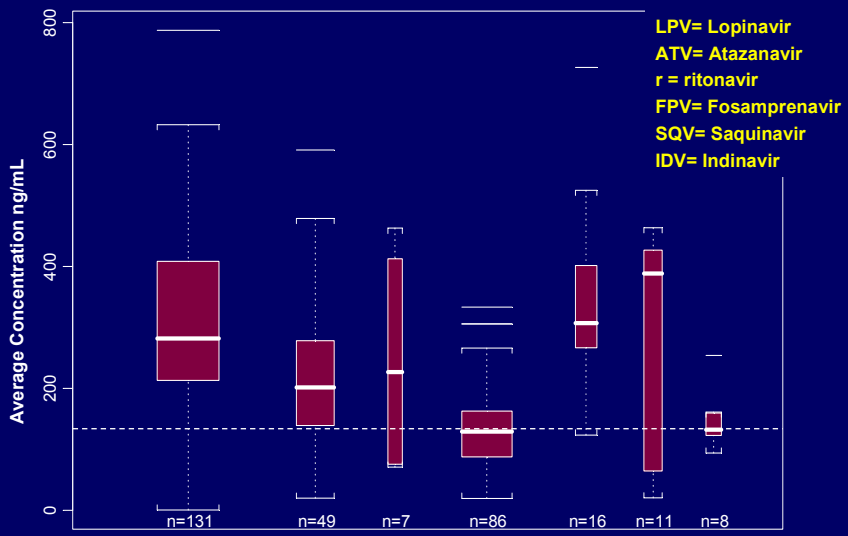
All ARV Experienced – 150 mg BID Group
Single PI vs. Phase 2a 300 mg BID



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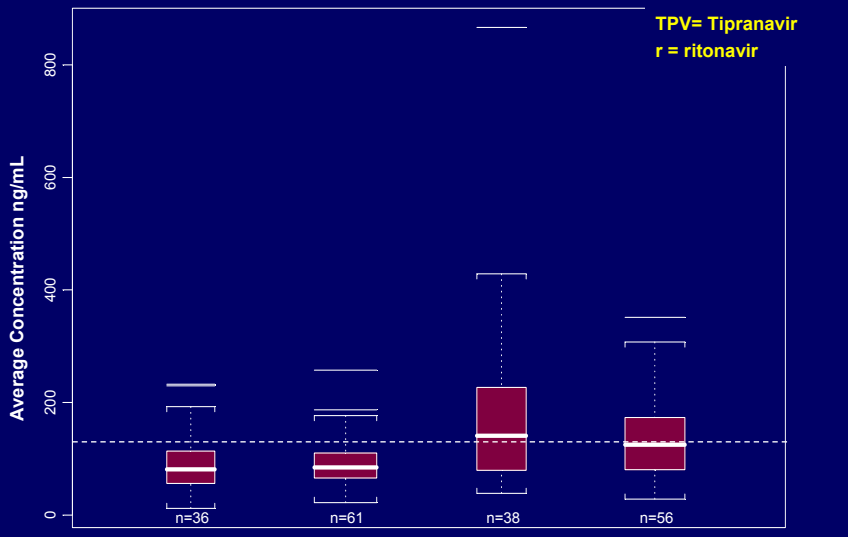
All ARV Experienced – 300 mg QD and BID
in the Presence and Absence of Tipranavir/ritonavir



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Exposure Response Efficacy Analysis
A4001027 and A4001028

- Endpoints
  - Virology
    - VL < 50 copies/mL at week 24
    - VL < 400 copies/mL at week 24
    - Failure at week 4: VL > 400 copies/mL or decrease from baseline less than -1 $\log_{10}$ copies/mL
  - CD4+ cell count change from baseline at week 24
- Method: Generalized additive modeling (GAM)
- Prognostic factors tested included:
  - Dose + compliance or C_{min}, or C_{av}
  - Baseline viral load, CD4, tropism phenotype
  - Number of active drugs, PI use, ENF use, etc
  - Demographics

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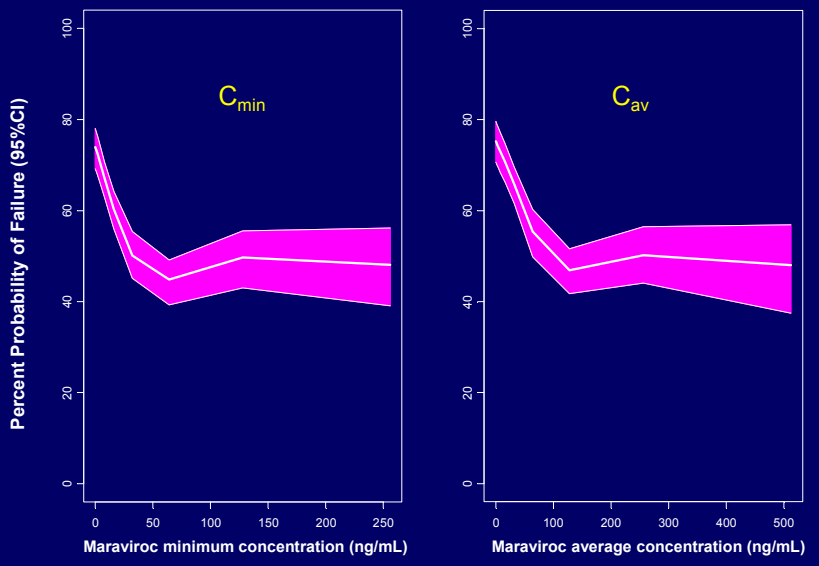
Probability of Failure (HIV-1 RNA > 50 c/mL)
As a Function of the MVC C_{min} and C_{av} (Week 24)



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Combined A4001027 and A4001028: Tropism Change

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Mean Change in CD4 Count from Baseline by Tropism Results in Treatment Failures

	Mean change in CD4 count (cells/mm^3)		
Tropism Result, Baseline → Treatment Failure	Placebo + OBT N=209	MVC QD + OBT N=414	MVC BID + OBT N=426
All treatment failures	+14 (n=97)	+49 (n=68)	+71 (n=77)
R5 → R5	+15 (n=80)	+61 (n=18)	+138 (n=17)
R5 → D/M or X4	+67 (n=4)	+37 (n=31)	+56 (n=32)
Non-R5 → Any	+15 (n=8)	+54 (n=11)	+26 (n=19)

A4001027 and A4001028

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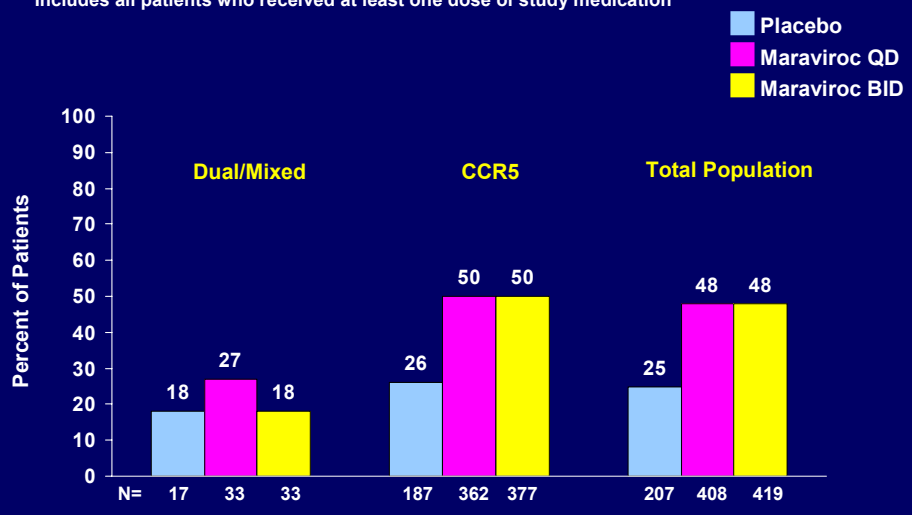
Patients with HIV-1 RNA < 50 c/mL
by Tropism at Baseline (Week 24)

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



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Tropism Results on Follow-up
in Patients Failing with D/M or X4-tropic HIV-1

Treatment	N	D/M or X4-tropic virus at last follow-up		R5-tropic virus at last follow-up	
		# of Patients	Median Days	# of Patients	Median Days
MVC All	44	14	16	30	203
MVC QD	23	9	11	14	182
MVC BID	21	5	121	16	207
Placebo	3	2	22	1	20

A4001027 and A4001028

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Overview

- Overview of the maraviroc Phase 2b/3 development program
- Clinical results in treatment-experienced patients with R5-tropic HIV-1
- Clinical results in treatment-experienced patients with dual/mixed-tropic HIV-1

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Demographics and Baseline Characteristics

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

Randomized N = 190 Treated N = 186	Placebo + OBT N=62	MVC QD + OBT N=63	MVC BID + OBT N=61
Mean age, yrs (range)	45 (23–65)	43 (16–59)	43 (16–62)
Male, n (%)	53 (86)	53 (84)	55 (90)
White, n (%)	40 (65)	46 (73)	44 (72)
Median CD4 count, cells/mm^3 (range)	42[1] (2, 650)	40[2] (1, 442)	43* (0, 615)
Mean HIV-1 RNA, $\log_{10}$ c/mL (range)	5.01[1] (3.65, 6.15)	5.03[2] (3.43, 5.94)	5.10* (3.61, 6.67)
Enfuvirtide in OBT, %	56	60	57
D/M at Screening, n	58	57	52

[1]N=58, [2]N= 57, *N=52, **N=54

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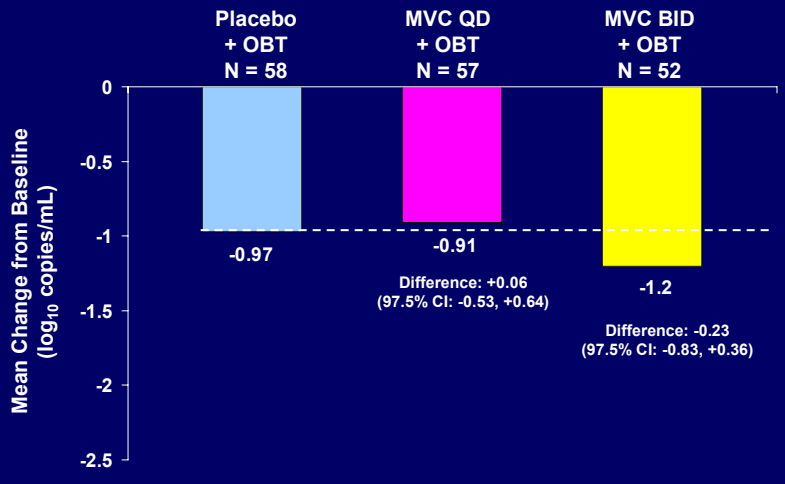
Mean Change in HIV-1 RNA from Baseline at Week 24

Includes all patients with D/M-tropic HIV-1 who received at least one dose of study medication



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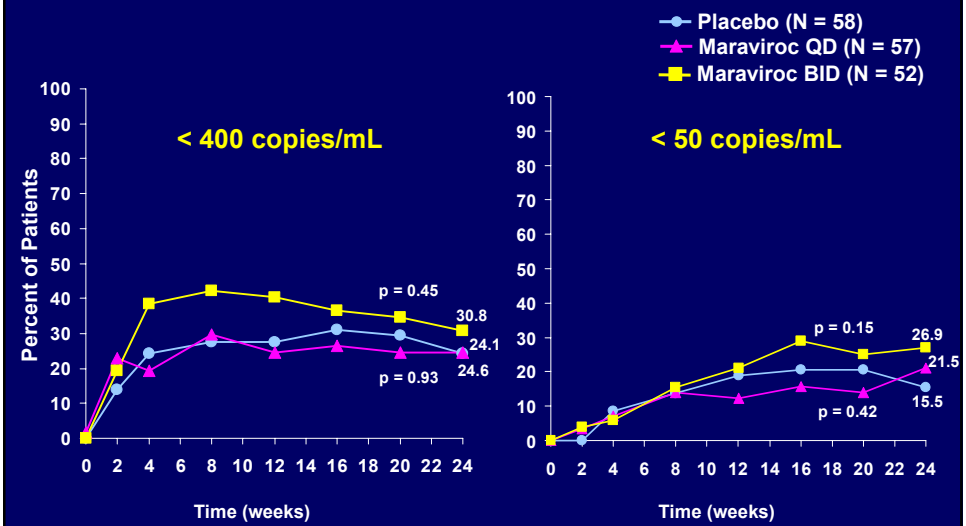
Patients with Undetectable HIV-1 RNA at Week 24

Includes all patients with D/M-tropic HIV-1 who received at least one dose of study medication



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Mean Change in CD4 Cell Count from Baseline

	cells/mm^3		
	Placebo + OBT	MVC QD + OBT	MVC BID + OBT
All treated patients with D/M-tropic HIV-1	+36* (n=58)	+60 (n=57)	+62 (n=52)
Difference MVC – Placebo (95% CI)	N/A	+24 (-1.36, 49.21)	+26 (0.87, 52.49)
Patients discontinuing due to treatment failure	+4 (n=23)	+38 (n=33)	+25 (n=21)
Patients with only X4-tropic HIV-1 detectable at time of treatment failure	-104 (n=2)	+48 (n=12)	+33 (n=12)

* Data for 4 patients is missing, D/M - dual/mixed-tropic, LOCF.
Mayer H et al. *16th IAC* 2006; abstract THLB0215

A4001029

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Summary

- In treatment-experienced patients with R5-tropic HIV-1 and few remaining treatment options, maraviroc + OBT demonstrated significantly greater virologic suppression and CD4 cell increases compared with placebo + OBT
- There are subgroups of patients where there appears to be an efficacy difference between maraviroc BID and maraviroc QD
  - HIV-1 RNA ≥ 100,000 c/mL
  - Very low CD4
  - No other active ARVs

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Summary

- Patients with R5-tropic HIV-1 failing on maraviroc had mean increases in CD4 count that were greater than placebo even when failing in the context of a change in tropism
- Of patients with R5-tropic virus at baseline who failed on maraviroc + OBT, nearly twice as many patients had a change in tropism to D/M-tropic or X4-tropic as compared with remaining R5-tropic
  - The virus in most patients who failed on maraviroc with D/M-tropic or X4-tropic virus reverted back to R5-tropic during the follow-up period

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Summary

- In treatment-experienced patients with D/M-tropic HIV-1, maraviroc + OBT did not lead to a significantly greater reduction in HIV-1 RNA, but was also not associated with an adverse virologic outcome and demonstrated greater CD4 increases as compared with placebo + OBT
  - These results were also observed in those patients (7.6%) in studies 1027 and 1028, who had a change in tropism from R5-tropic to D/M-tropic between screening and baseline

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Agenda and Speakers

- Introductions, Background and Overview of Maraviroc
  Michael Dunne MD, Therapeutic Area Head, Development, Infectious Diseases
- Clinical Efficacy
  Howard Mayer MD, Global Clinical Leader, Pfizer
- **Safety and Toleration**
  Steve Felstead MB ChB, Maraviroc Team Leader, Pfizer
- *In Vitro* and *In Vivo* Tropism and Resistance Evaluation
  Mike Westby PhD, Virology Team Leader, Pfizer
- Medical Need and Place in HIV Armamentarium
  Dan Kuritzkes MD, Brigham and Women's Hospital, Harvard Medical School, Boston
- Conclusions
  Michael Dunne MD

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Safety and Toleration of Maraviroc

Steve Felstead, MB ChB
Pfizer Global Research & Development

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