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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Safety and Toleration of Maraviroc

- Safety and Toleration in Phase 1/2a
- Safety and Toleration in Phase 2b/3
  - Exposure to maraviroc
    - Adverse event overview
  - Cardiovascular safety evaluation
    - Postural hypotension
    - QTc
    - Ischemic adverse events
  - Hepatic safety evaluation
  - Immune function safety evaluation
    - Category C events
      - Infection
      - Malignancies
  - Mortality
- Conclusions

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Summary of Subject Exposure
Phase 1/2a Studies

	Maraviroc	Placebo
Phase 1		
Single dose	299	-
Multiple dose	333	-
Phase 2a	66	16
Total Short Term Studies	698	16

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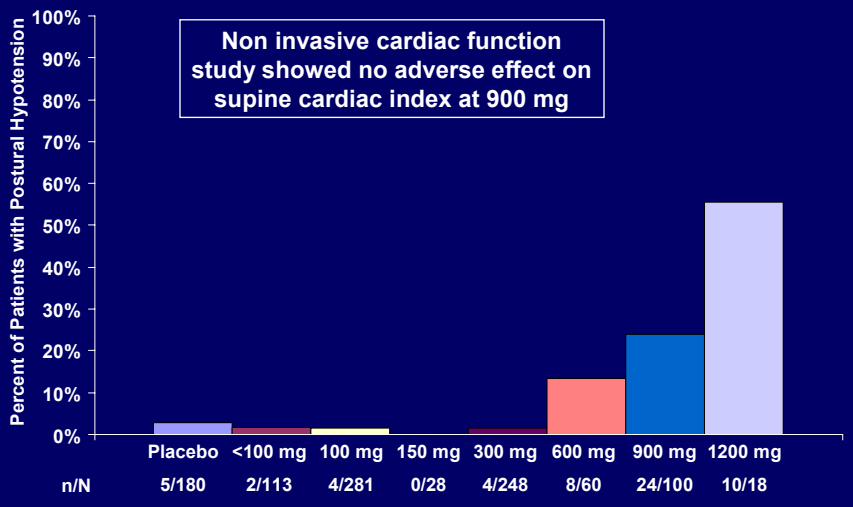
Postural Hypotension
Phase 1/2a



Any of the following: decrease in supine to standing BP of ≥10 mmHg (diastolic) or ≥20 mmHg (systolic), or a standing systolic BP of <90 mmHg

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QTc Evaluation

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QTc Interval in Healthy Subjects
1016

- Randomized, placebo-controlled, crossover study
  - 61 healthy volunteers
- Single doses of maraviroc (100 mg, 300 mg, and 900 mg) and moxifloxacin 400 mg
  - Mean difference in QTcI from placebo was <4 msec (upper 90% CI <7 msec)
  - Moxifloxacin caused a mean increase in QTcI of 12-14 msec
- PK/PD modeling predicts a 1 msec change in QT per 1000 ng/ml (maximum concentration studied 2360 ng/ml)

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Safety and Toleration Summary
Phase 1/2a

- Maraviroc well tolerated at unit doses of up to 300 mg
- Postural hypotension identified as dose limiting toxicity with frequency > placebo at maraviroc unit doses of 600 mg and above
- No clinically relevant effect on QTc

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Safety and Toleration of Maraviroc

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Summary of Subject Exposure
Phase 2b/3

	Maraviroc	Comparator
Phase 2b/3		
Treatment Experienced R5 patients (1027 & 1028)	840	209
Treatment Experienced nonR5 patients (1029)	124	62
Total Treatment Experienced patients	**964**	**271**
Open Label from placebo (1027 & 1028)	74	-
Naïve, QD regimen (1026)	174	-
Total Phase 2b/3 Studies	**1212**	**271**

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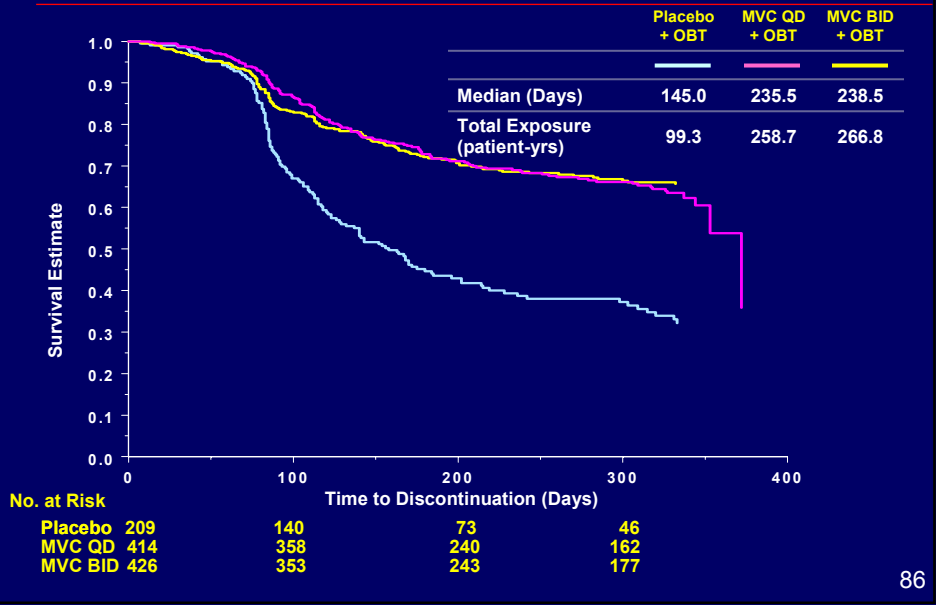
Time to Discontinuation
1027/1028



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Summary of AEs, SAEs, and Discontinuations 1027/1028

	Placebo + OBT	MVC QD + OBT	MVC BID + OBT
Number of Patients treated (N)	209	414	426
Patient years exposure (PYE)	99	259	267
Patients with AEs: %	83.7	88.4	89.9
Patients discontinuing due to AEs: %	3.8	4.8	4.0
Patients with SAEs: %	16.3	14.0	15.7
Category C events n	16	29	19
Subjects with Cat C: %	6.7	6.3	4.2
Deaths*: %	0.5	1.4	1.2

* Reported on double blind medication or within 28 days of discontinuation from study drug

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Summary of AEs, SAEs, and Discontinuations 1029

	Placebo + OBT	MVC QD + OBT	MVC BID + OBT
Number of Patients treated (N)	62	63	61
Patient years exposure (PYE)	25	26	28
Patients with AEs: %	88.7	85.7	91.8
Patients discontinuing due to AEs: %	6.5	3.2	4.9
Patients with SAEs: %	16.1	14.3	14.8
Category C events n	3	7	3
Subjects with Cat C: %	3.2	9.5	4.9
Deaths*: %	3.2	3.2	1.6

* Reported on double blind medication or within 28 days of discontinuation from study drug

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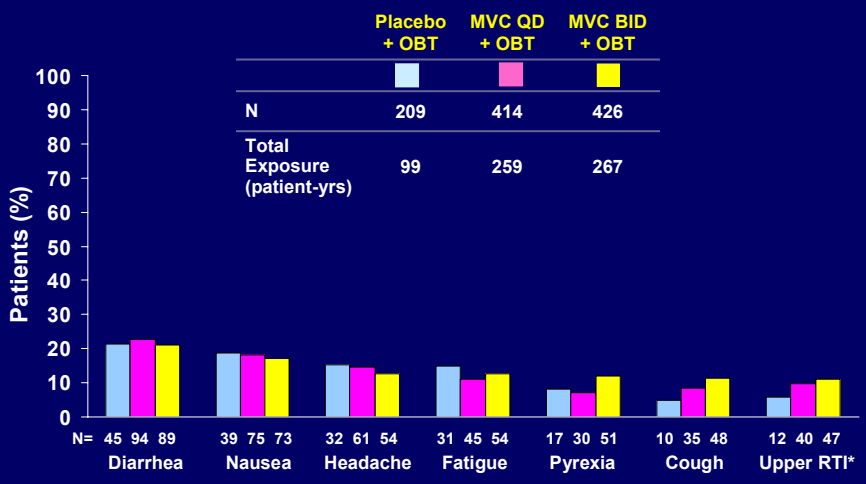
Incidence of AEs Occurring in ≥ 10% of Patients in Any Group Unadjusted for Exposure - 1027/1028



* URTI and viral URTI merged and assumed to be individual patients

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Safety and Toleration of Maraviroc

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Patients with Postural Hypotension*
1027/1028/1029

	Placebo + OBT n/N (%)	MVC QD + OBT n/N (%)	MVC BID + OBT n/N (%)
Baseline	6/235 (2.6)	15/399 (3.8)	14/423 (3.3)
Week 2	11/251 (4.4)	27/446 (6.1)	33/462 (7.1)
Week 24	5/117 (4.3)	16/311 (5.1)	19/323 (5.9)
Unplanned	1/11 (9.0)	0/11	1/17 (5.9)
Early Termination	6/89 (6.7)	4/79 (5.1)	8/95 (8.4)

* Any of the following: decrease in supine to standing BP of ≥10 mmHg (diastolic) or ≥20 mmHg (systolic), or a standing systolic BP of <90 mmHg

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Mean Baseline QTcF Intervals and Change from Baseline
1027/1028/1029

	Placebo + OBT QTcF msec (N*)	MVC QD + OBT QTcF msec (N*)	MVC BID + OBT QTcF msec (N*)
Baseline	403.6 (186)	404.6 (360)	404.5 (386)
Change at Week 24	2.2 (63)	1.7 (156)	1.3 (159)
Change at Unplanned assessment	1.7 (10)	-2.0 (20)	2.8 (18)
Change at Early Termination	0.9 (82)	-1.9 (67)	-3.6 (73)

* Number of patients assessed at each time point

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Ischemic Adverse Events (All-Causality)
1027/1028/1029

% of Patients Reported with :	Placebo N=271 PYE=124 %	Placebo N=271 PYE=124 Exposure adjusted	MVC QD N=477 PYE=285 %	MVC QD N=477 PYE=285 Exposure adjusted	MVC BID N=487 PYE=295 %	MVC BID N=487 PYE=295 Exposure adjusted
Angina pectoris	0	0	0.4	0.7	0.2	0.3
Angina unstable	0	0	0.2	0.4	0.2	0.3
Coronary artery disease	0	0	0.4	0.7	0	0
Coronary artery occlusion	0	0	0.4	0.7	0	0
Myocardial infarction*	0	0	0.6	1.1	0.2	0.3
Myocardial ischemia	0	0	0	0	0.4	0.7
Prinzmetal angina	0	0	0	0	0.2	0.3
CVA	0	0	0.2	0.4	0.2	0.3
TIA	1.1	2.4	0	0	0	0
Cerebrovascular hemorrhage	0	0	0.2	0.4	0	0

*Includes presumptive MI
Overall MI rate is estimated on maraviroc to be 0.69/100PYE

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Maraviroc Cardiovascular Safety Evaluation Summary

- Maraviroc is associated with only a slight excess of measured postural hypotension compared to placebo – supporting the dose adjustment strategy
- Maraviroc is not associated with QTcF prolongation
- More ischemic adverse events were observed on maraviroc than placebo but event rate was consistent with expected for this heavily pre-treated population

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Maximum Liver Function Test Values (Grades 3 and 4) Without Regard to Baseline – 1027/1028

Percentage of patients with abnormalities	Placebo + OBT N=207*	MVC QD + OBT N=408*	MVC BID + OBT N=421*
Discontinuations due to Hepatic Adverse events: %	1	1	1.2
AST (IU/L): %			
Grade 3 (5.0–10.0 x ULN)	2.9	2.7	3.1
Grade 4 (>10.0 x ULN)	0	0.7	1.4
ALT (IU/L): %			
Grade 3 (5.0–10.0 x ULN)	2.9	3.4	1.4
Grade 4 (>10.0 x ULN)	0.5	0.5	1.0
Total bilirubin (mg/dL): %			
Grade 3 (2.5–5.0 x ULN)	3.9	7.1	5.0
Grade 4 (>5.0 x ULN)	1.5	1.0	0.7

* Number of patients with at least one on drug follow-up assessment

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Maximum Liver Function Test Values (Grades 3 and 4) Without Regard to Baseline – 1029

Percentage of patients with abnormalities	Placebo + OBT N=58*	MVC QD + OBT N=63*	MVC BID + OBT N=61*
AST (IU/L): %			
Grade 3 (5.0–10.0 x ULN)	3.4	1.6	1.6
Grade 4 (>10.0 x ULN)	0	1.6	0
ALT (IU/L): %			
Grade 3 (5.0–10.0 x ULN)	3.4	1.6	0
Grade 4 (>10.0 x ULN)	1.7	0	0
Total bilirubin (mg/dL): %			
Grade 3 (2.5–5.0 x ULN)	8.6	7.9	8.2
Grade 4 (>5.0 x ULN)	1.7	0	0

* Number of patients with at least one on drug follow-up

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Hepatic Safety Evaluation in Key Subgroups

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Maximum ALT (with Tipranavir) and Total Bilirubin (with Atazanavir) Values Grades 3 and 4 without Regard to Baseline – 1027/1028

Tipranavir +	Placebo + OBT n/N (%)*	MVC QD + OBT n/N (%)*	MVC BID + OBT n/N (%)*
ALT (IU/L) (>2.5XULN)	3/29 (10.3)	4/65 (6.2)	2/62 (3.2)

Atazanavir +	Placebo + OBT n/N (%)*	MVC QD + OBT n/N (%)*	MVC BID + OBT n/N (%)*
Total bilirubin (mg/dL) (>2.5XULN)	11/39 (28.2)	30/78 (38.5)	18/66 (27.3)

* Number of patients with at least one on drug follow up assessment

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Maximum ALT Abnormalities (Grade 3 or 4) in Co-infected Patients – 1027/1028/1029

	Placebo N=271	MVC QD N=477	MVC BID N=487
% of Patients with HCV RNA detectable	7.4	4.2	6.2
HCV Patients with ALT Abnormalities: n/N (%)	1/20 (5)	3/20 (15)	2/30 (6.7)
% of patients with HBV surface antigen positive	8.1	5.5	6.4
HBV Patients with ALT abnormalities: n/N (%)	2/22 (9.1)	0/26	1/31 (3.2)

Patients diagnosed as co-infected with at least one on drug follow up assessment

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Hepatic Safety Summary

- Maraviroc has no association with liver enzyme abnormalities in treatment experienced studies
- Adding Maraviroc to tipranavir or atazanavir does not increase the frequency of observed LFT abnormalities
- Maraviroc is not associated with an increase in abnormal LFTs in co-infected patients, but the number assessed is too small for firm conclusions

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Category C Events – Infections
1027/1028

Percentage of Patients reported with	Placebo + OBT N=209 PYE=99	MVC QD + OBT N=414 PYE=259	MVC BID + OBT N=426 PYE=267
Any Cat C Infection (/100PYE)	6.7(9.4)	6.3 (9.2)	4.2 (6.1)
Herpes Simplex	1.0	2.4	1.4
Esophageal Candidiasis	1.0	2.9	0.7
Pneumocystis jirovecii Pneumonia	0	0	0.5
Cytomegalovirus Infection*	0	0.5	0.5
Mycobacterium avium complex	1.4	0	0.2
Mycobacterial Infection	0	0	0.2
Recurrent Bacterial Pneumonia	1.0	0.2	0
Cryptosporidium Enteritis	0.5	0	0
Progressive Multifocal Leukoencephalopathy	0	0	0.2

* Includes CMV infection, CMV gastrointestinal infection and CMV retinitis

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Infections of Interest* Occurring in ≥ 2% of Patients in Any Dose Group – 1027/1028

% of patients* reported with	Placebo + OBT		MVC QD + OBT		MVC BID + OBT	
	N=209	PYE=99	N = 414	PYE=259	N = 426	PYE=267
	%	Exposure Adjusted	%	Adjusted Exposure	%	Adjusted Exposure
Any infections	38.3	118.2	47.8	120.7	50.2	125.9
Herpes simplex	3.8	8.1	4.3	7.2	6.8	11.4
Candidiasis	5.7	12.2	8.2	13.5	4.0	6.5
URTI	5.7	12.6	9.7	16.6	11.0	18.8
Pharyngitis	5.7	12.4	8.5	14.2	8.5	14.2
Influenza	0.5	1.0	4.3	7.1	1.6	2.7
Bronchitis	4.3	9.3	6.3	10.5	6.1	10.1
Pneumonia	5.3	11.2	3.1	5.1	2.1	3.5
Sinusitis	3.3	7.3	3.9	6.4	6.1	10.1

* Related terms have been merged and assumed to be in individual patients

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Category C Events – Malignancies
1027/1028

	Placebo + OBT N=209 PYE=99	MVC QD + OBT N=414 PYE=259	MVC BID + OBT N=426 PYE=267
Kaposi's Sarcoma n (%)	3 (1.4)	1 (0.2)	2 (0.5)
Lymphoma n (%)	2 (1.0)	2 (0.5)	1 (0.2)*

- 1027-Placebo – Large cell lymphoma
- 1027-Placebo – Large B cell lymphoma
- 1027-MVC QD – B cell lymphoma (start date = day 25)
- 1028-MVC QD – Non-Hodgkin's lymphoma
- 1028-MVC BID – B cell lymphoma (start date = day 7)
- ** 1027-Placebo → OL MVC BID– B cell lymphoma not included*
- ** 1028-MVC BID – CNS lymphoma (presumed) not included*

No lymphomas were reported in Study 1029

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Incidence of Other Malignancies
1027/1028

Percentage of patients reported with	Placebo + OBT N=209 PYE=99	MVC QD + OBT N=414 PYE=259	MVC BID + OBT N=426 PYE=267
Anal Carcinoma	1.4	0.7	0.7
Basal Cell CA	0	0.2	0.2
Bowens Disease	0	0	0.2
Liver Metastases	0	0.2	0
Esophageal CA	0	0.2	0
Squamous Cell CA	0.5	0.2	0
SCC of Skin	0	0.2	0
Sweat Gland Tumor	0	0	0.2
Tongue Neoplasm	0	0	0.2

No imbalance of reported malignancies was observed in Study 1029

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Immune Function Safety Summary

- Maraviroc is not associated with an excess of Category C infections or malignancies (including lymphoma) compared to placebo
- Maraviroc is not associated with other malignancies
- Maraviroc may be associated with an excess of upper respiratory tract infections and mild HSV

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Summary of All Deaths and Deaths on Treatment 1027/1028/1029

Study	Placebo (N= 271)	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Maraviroc BID OL (N=109)	ISOD
All Deaths Irrespective of Time On or Off Study Treatment					
1027	2	2	1	2	1
1028	0	5	5	0	0
1029	3	2	2	0	0
Total	5 (1.8%)	9 (1.9%)	8 (1.6%)	2	1
Deaths Occurring on Study Drug or Within 28 Days of Discontinuing Double Blind Study Treatment					
1027	1	2	1		
1028	0	4	4		
1029	2	2	1		
Total	3 (1.1%)	8 (1.7%)	6 (1.2%)		

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Summary of Deaths and Exposure Adjusted Mortality Rate – 1027/1028/1029

Treatment Group	N	Patient Year Exposure	Deaths on DB or within 28 days n (%)	Deaths on DB or within 28 days MR/100PYE
Placebo	271	124.3	3 (1.1)	2.4
MVC QD	477	285.1	8 (1.7)	2.8
MVC BID	487	294.7	6 (1.2)	2.0
All MVC	964	579.8	14 (1.5)	2.4

DB = double blind

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Mortality in Maraviroc Trials

- Mortality rates were similar to historical data from similar studies
- Causes of death are as expected for the population studied, with no single reason observed
- There is no evidence for a contribution of maraviroc to mortality

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Maraviroc Safety and Toleration Conclusions 1

- Maraviroc BID + OBT is as well tolerated as maraviroc QD + OBT
- Adverse events on maraviroc are similar in frequency and nature to placebo + OBT
- Maraviroc is associated with a slight excess of postural hypotension at 300 mg or 150 mg (in presence of a CYP3A4 inhibitor)
- Maraviroc is not associated with QTc prolongation
- Ischemic adverse events were seen more frequently in the maraviroc treatment arms but event rates were consistent with expected rates in a heavily pre-treated population

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Maraviroc Safety and Toleration Conclusions 2

- Maraviroc is not associated with elevations in hepatic enzymes in treatment experienced studies
- Maraviroc is not associated with an excess of Category C events
- Maraviroc may be associated with an excess of upper respiratory tract infections and mild HSV
- Maraviroc is not associated with excess mortality compared to placebo

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