

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008;359:1429-41.

WEB-ONLY SUPPLEMENT

Methods:

Due to an administrative error, two randomized patients in MOTIVATE 2 received incorrect study treatment for 4 weeks, one randomized to maraviroc twice-daily received placebo and one randomized to placebo received maraviroc twice-daily. Efficacy results were qualitatively similar including or removing these patients from the analyses.

A single pre-planned 24-week analysis of safety and efficacy was conducted by the study team and reviewed by the independent Data and Safety Monitoring Board who recommended that the study should continue unchanged.

Acknowledgments:

MOTIVATE 1 SITE INVESTIGATORS

Canada

Jonathan Angel, Brian Conway, Kevin A. Gough, Richard G. Lalonde, Francois Laplante, Roger P. Leblanc, Julio S.G. Montaner, Anita R. Rachlis, Barbara Romanowski, Stuart J. Rosser, Ethan Rubinstein, Stephen David Shafran, Fiona Smail, Cecile Tremblay, Benoit Trottier, Sylvie Trottier, Christos Tsoukas, Sharon Lynn Walmsley

United States of America

Alen Voskanian, Bisher Akil, Roberto Claudio Arduino, David Asmuth, George William Beatty, Stephen Lawrence Becker, Nicholaos C. Bellos, Sky Robert Blue, Robert Key Bolan, John D. Brand, George Ghazaros Burnazian, Alfred F. Burnside, Thomas B. Campbell, Rafael E. Campo, Kathleen King Casey, Paul Joseph Cimoch, Calvin J. Cohen, Gregg Oscar Coodley, Roberto B. Corales, Edwin DeJesus, Leslie E. Diaz, George L. Drusano, Jerome A. Ernst, Judith E. Feinberg, Lawrence Edward Feldman, Steven M. Fine, Jason Andrew Flamm, Stephen Eliot Follansbee, Todd Allen Fralich, Emanuel Gallant, Eliot Warren Godofsky, Gary Green, Paula Rosa Greiger-Zanlungo, Barbara Marie Gripshover, Richard K. Groger, Roy Gulick, William David Hardy, Shawn K. Hassler, Richard Harold Haubrich, Stephen P. Hauptman, David Holden Henry, William Keith Henry, Jose Norberto Hernandez, Charles Byron Hicks, Michael Alan Horberg, Joseph G. Jemsek, Allan Rowan Kelly, Clifford A. Kinder, Daniel Benjamin Klein, Laura Kogelman, Jacob Paul Lalezari, Anthony LaMarca, Harry William Lampiris, Matthew Leibowitz, Jason Mark Leider, Jeffrey Lloyd Lennox, Ralph Liporace, Harold Luther Martin, Lucia M. Martinez-Bejar., Claudia Martorell, Joseph P. McGowan, Donna Mildvan, Steven Miles, Ronald Takeshi Mitsuyasu, Javier Osvaldo Morales-Ramirez, Anne B. Morris, Karam Chucri Mounzer, Robert Anderson Myers, Jeffrey P. Nadler, Daniel Pearce, Gerald Pierone, Bruce Stephen Rashbaum, Jayashree Ravishankar, Robert Ray Redfield, Richard Craig Reichman, William Jay Robbins, Stockton Edward Roberts, Jorge E. Rodriguez, Michael Saag, Kunthavi Sathasivam, Paul Edward Sax, Lawrence E. Schwartz, Sorana Segal-Maurer, Michael Grant Sension, Gladys E. Sepulveda-Arzola, Paul Richard Skolnik, Louis Marshall Sloan, Robert P. Smith, James Michael Sosman, Jack Thomas Stapleton, Roy Steigbigel, Corklin R. Steinhart, Donna Elaine Sweet, Susan Swindells, Pablo Tebas, Melanie Ann Thompson, Silver Sisneros, William James Towner, Peter Gordon. Trevor N. Hawkins, David Allen Wheeler, Sally Williams, Dean Wilcox, Steven Williams, Todd Stephen Wills, Michael Bruce Wohlfeiler, David Wright, Angela Xavier, Bienvenido Gamulo Yangco, Barry Stephen Zingman, Carmen D. Zorrilla

MOTIVATE 2 SITE INVESTIGATORS

Australia

Anthony M. Allworth, Mark T. Bloch, Neil J. Bodsworth, John Chuah, David Cooper, Nicholas Doong, Dominic Dwyer, Julian Gold, Jennifer Frances Hoy, Richard J. Moore, Norman J. Roth, Cassy Workman

Belgium

Nathan Clumeck, Patricia Dellot, Jean Christophe Goffard, Michel Moutschen,
Bernard C. Vandercam, Dirk Vogelaers

Canada

Danielle Rouleau

France

Michele Bentata, Laurent Cotte, Jean-Francois Delfraissy, Jacques Durant, Pierre-
Marie Girard, Laurent Hocqueloux, Roland Landman, Alain Lafeuillade, Isabelle
Poizot Martin, Jean-Michel Molina, Gilles Pialoux, Christophe Piketty, Francois Raffi,
Jacques Reynes, Renaud Verdon

Germany

Keikawus Arasteh, Johannes Richard Bogner, Norbert H. Brockmeyer, Stefan
Esser, Gerd Fätkenheuer, Frank-Detlef Goebel, Thomas Harrer, Peter Kern,
Heribert Knechten, Jan van Lunzen, Markus Mueller, Antonius Mutz, Mark Oette,
Andreas Plettenberg, Juergen Rockstroh, Jorg-Andres Rump, Reinhold E. Schmidt,
Lothar Schneider, Dieter Schuster, Schlomo Staszewski, Hans-Juergen Stellbrink,
Andreas Trein, Lutwinus Weitner

Italy

Fernando Aiuti, Dante Bassetti, Antonio Di Biagio, Pietro Caramello, Giampiero
Carosi, Roberto Esposito, Adriano Lazzarin, Francesco Leoncini, Paolo Emilio
Manconi, Francesco Mazzotta, Francesco Montella, Enzo Raise, Vincenzo Vullo

Netherlands

Ilija Mohandas Hoepelman, Rosalinde Maria Perenboom, J. M. Prins, Clemens
Richter, Marchina Elisabeth Van Der Ende

Poland

Marek Beniowski, Anna Boron-Kaczmarska, Robert Flisiak, Waldemar Halota,
Andrzej Horban, Tomasz Mach, Tomasz Smiatacz

Spain

Fernando Lozano de Leon, Pompeyo Viciano Fernandez, Rafael Rubio Garcia,
Jose Josep Gatell Artigas, Juan Julian Gonzalez Garcia, Felix Gutierrez, Juan
Gonzalez Lahoz, Jose Iribarren Loyarte, Santiago Moreno, Federico Pulido Ortega,
Pere Domingo Pedrol, Antonio Rivero, Bonaventura Clotet, Cristina Sarria

Sweden

Magnus Gisslen, Leo Flamholz, Anders Karlsson

Switzerland

Manuel Battegay, Enos Bernasconi, Matthias Cavassini, Henning Drechsler,
Bernard Hirschel, Milos Opravil, Pietro Vernazza

United Kingdom

Philippa Jane Easterbrook, Martin Fisher, Philip Hay, Margaret A. Johnson, Clifford
L. Leen, Mark R. Nelson, Edmund Ong, Jonathan N. Weber, David J. White,
Edmund Wilkins, Martin Wiselka

United States

Ana Maria Alvarez-Jacinto, Diana Antoniskis, Barbara A. Atkinson, Daniel S. Berger, Gary Blick, Robert Owen Brenna, Jeffrey Howard Burack, L. W. Preston Church, Patrick G. Clay, Paul Peniston Cook, Catherine Maria Creticos, Patrick William Daly, Getachew Feleke, Thomas Mc Donald File, Jeffrey Eliot Galpin, Stephen Lloyd Green, Frances Fae Haas, Barbara J. Hanna, Chiu-Bin Hsiao, Ricky K. Hsu, Robert S. Jones, Peter Kadlecik, Robert Charles Kalayjian, Robert H. Keller, Shubha Kerkar, Janak Koirala, Leon Liang-Yu Lai, Sujata Lalla-Reddy, Rodger David Macarthur, Gregory John Malanoski, Norman Peter Markowitz, Patrick L. McLeroth, Alexander A. McMeeking, Goran Miljkovic, John Buscemi Montana, Daniel Edward Nixon, Dorece G. Norris, Jesse Pullen Penico, Leonel Perez-Limonte, Lynette H. Posorske, David James Prelutsky, James Riddell, Barry Michael Rodwick, Peter Jerome Ruane, James Sampson, Steven Santiago, Amy Seinfeld, Victoria Lee Sharp, Zaher Shebib, Mark Leslie Tanner, Joseph G. Timpone, Barbara H. Wade, Frances Wallach, Winkler Weinberg, Christine Zurawski

Supplemental Table 1: Grade 3/4 Laboratory Events (combined MOTIVATE 1 & 2 data)*

		Placebo + OBT	Maraviroc QD + OBT	Maraviroc BID + OBT
		N=207	N=408	N=421
Clinical Chemistry				
glucose (fasting): hypoglycemia	Grade 3 (30-39 mg/dL)	0	1 (0.2%)	0
	Grade 4 (<30 mg/dL)	0	0	0
amylase	Grade 3 (>2.0–5.0x ULN)	12 (5.8%)	26 (6.4%)	24 (5.7%)
	Grade 4 (>5.0x ULN)	0	3 (0.7%)	1 (0.2%)
lipase	Grade 3 (>2.0–5.0x ULN)	7 (7.7%)	13 (7.7%)	8 (5.0%)
	Grade 4 (>5.0x ULN)	0	1 (0.6%)	2 (1.3%)
Electrolytes				
sodium (hypernatremia)	Grade 3 (158-165 mEq/L)	0	0	0
	Grade 4 (>165 mEq/L)	0	0	0
sodium (hyponatremia)	Grade 3 (116-122 mEq/L)	0	1 (0.2%)	1 (0.2%)
	Grade 4 (<116 mEq/L)	0	0	0
potassium (hyperkalemia)	Grade 3 (6.6-7 mEq/L)	0	1 (0.2%)	0
	Grade 4 (>7.0 mEq/L)	0	0	0
potassium (hypokalemia)	Grade 3 (2-2.4 mEq/L)	0	1 (0.2%)	0
	Grade 4 (<2 mEq/L)	0	0	0
calcium [†] (hypercalcemia)	Grade 3 (12.6-13.5 mg/dL)	0	0	0
	Grade 4 (>13.5 mg/dL)	0	0	0
calcium [†] (hypocalcemia)	Grade 3 (6.1-6.9 mg/dL)	0	2 (0.5%)	2 (0.5%)
	Grade 4 (<6.1 mg/dL)	1 (0.5%)	0	0
Hematology				
hemoglobin	Grade 3 (6.5-6.9 g/dL)	0	1 (0.2%)	1 (0.2%)
	Grade 4 (<6.5 g/dL)	0	2 (0.5%)	1 (0.2%)
platelets	Grade 3 (20-49 10 ³ /mm ³)	2 (1.0%)	2 (0.5%)	1 (0.2%)
	Grade 4 (<20 10 ³ /mm ³)	0	0	0
absolute neutrophil count	Grade 3 (500-749/mm ³)	5 (2.4%)	6 (1.5%)	13 (3.1%)
	Grade 4 (<500/mm ³)	0	3 (0.7%)	5 (1.2%)
Renal Function				
creatinine	Grade 3 (>3x-6x ULN)	1 (0.5%)	3 (0.7%)	1 (0.2%)
	Grade 4 (>6x ULN)	0	0	0

* Irrespective of baseline grade. There was no evidence of significant differences among study arms. Comparisons are post-hoc and unadjusted for duration of treatment exposure or multiple testing.

[†] corrected for albumin

OBT, optimized background therapy; x, times; ULN, upper limit of normal

Supplemental Table 2: Grade 1-4 hepatic laboratory test abnormalities (combined MOTIVATE 1 & 2 data)*

		Placebo+ OBT N=207	Maraviroc QD + OBT N=408	Maraviroc BID + OBT N=421
AST	Grade 1	77 (37%)**	125 (31%)**	110 (26%)**
	Grade 2	17 (8%)	34 (8%)	44 (10%)
	Grade 3	6 (3%)	12 (3%)	14 (3%)
	Grade 4	0	4 (1%)	6 (1%)
ALT	Grade 1	63 (30%)	120 (29%)	103 (24%)
	Grade 2	15 (7%)**	20 (5%)**	43 (10%)**
	Grade 3	6 (3%)	16 (4%)	7 (2%)
	Grade 4	1 (0.5%)	2 (0.5%)	4 (1%)
bilirubin (total)	Grade 1	18 (9%)	34 (8%)	36 (9%)
	Grade 2	22 (11%)	35 (9%)	32 (8%)
	Grade 3	8 (4%)	28 (7%)	21 (5%)
	Grade 4	3 (1%)	5 (1%)	2 (0.5%)
alkaline phosphatase	Grade 1	24 (12%)	52 (13%)	45 (11%)
	Grade 2	1 (0.5%)	13 (3%)	11 (3%)
	Grade 3	0	1 (0.2%)	1 (0.2%)
	Grade 4	0	1 (0.2%)	0

AST, ALT and Alkaline Phosphatase

Grade 1: $\geq 1.25x - \leq 2.5x$ ULN
 Grade 2: $> 2.5x - \leq 5.0x$ ULN
 Grade 3: $> 5.0x - \leq 10.0x$ ULN
 Grade 4: $> 10.0x$ ULN

Bilirubin

Grade 1: $> 1.0x - \leq 1.5x$ ULN
 Grade 2: $> 1.5x - \leq 2.5x$ ULN
 Grade 3: $> 2.5x - \leq 5.0x$ ULN
 Grade 4: $> 5.0x$ ULN

* Irrespective of baseline grade. There was no evidence of significant differences among study arms, except as noted. Comparisons are post-hoc and unadjusted for duration of treatment exposure or multiple testing.

** P=0.02

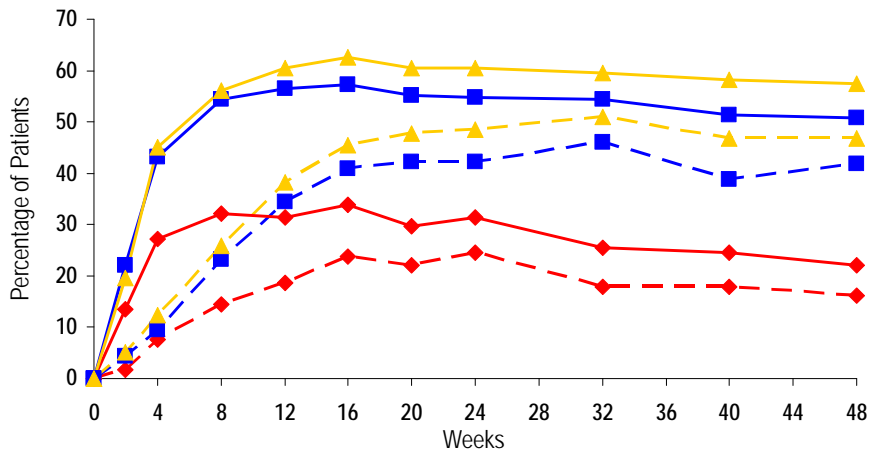
OBT, optimized background regimen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; x, times; ULN, upper limit of normal

Supplemental Figure 2: Treatment Responses over 48 Weeks*

(A) HIV-1 RNA Suppression †

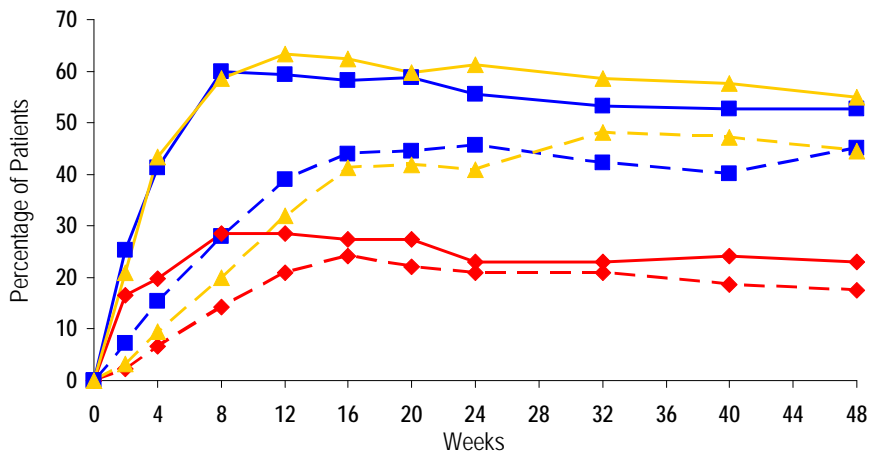


MOTIVATE 1



PBO	n=	118	115	111	95	71	59	58	50	46	42
MVC QD	n=	232	223	217	202	182	176	166	157	152	143
MVC BID	n=	232	223	217	209	191	178	172	164	160	152

MOTIVATE 2

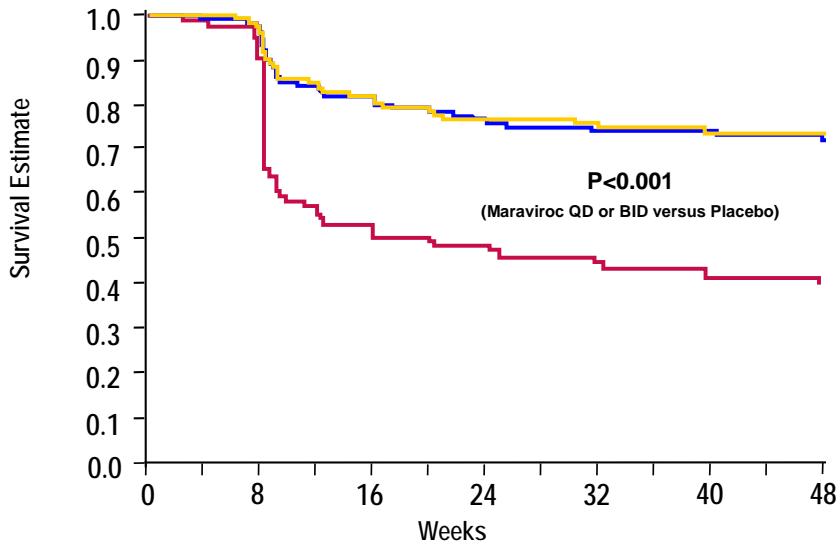


PBO	n=	91	90	82	77	56	48	40	34	32	30
MVC QD	n=	182	176	173	166	150	137	130	125	119	113
MVC BID	n=	191	179	181	170	150	140	142	133	126	129

(B) Time to Protocol-Defined Treatment Failure

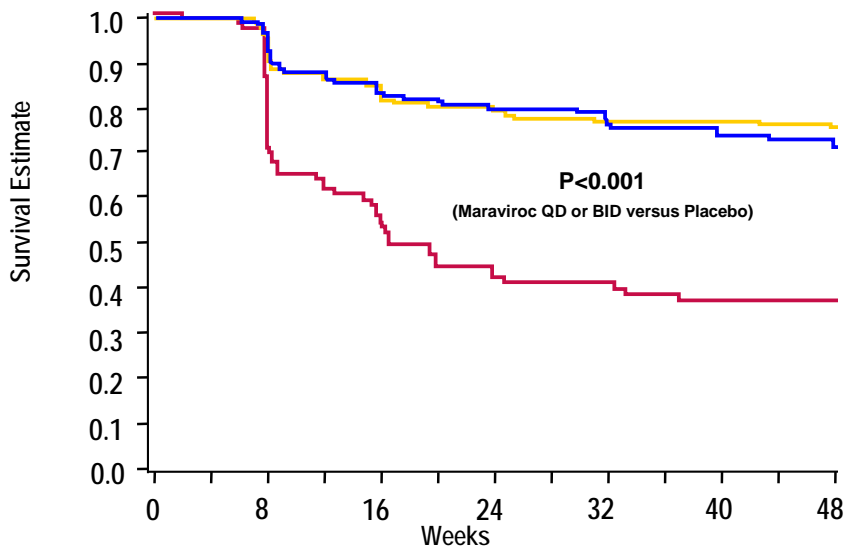
— Placebo plus OBT
 — Maraviroc, once daily plus OBT
 — Maraviroc, twice daily plus OBT

MOTIVATE 1



PBO	n=	118	114	103	64	58	54	52	49	48	43	43	39	33
MVC QD	n=	232	226	214	183	176	169	161	157	153	150	146	142	115
MVC BID	n=	235	224	215	188	179	171	166	163	160	158	157	151	119

MOTIVATE 2

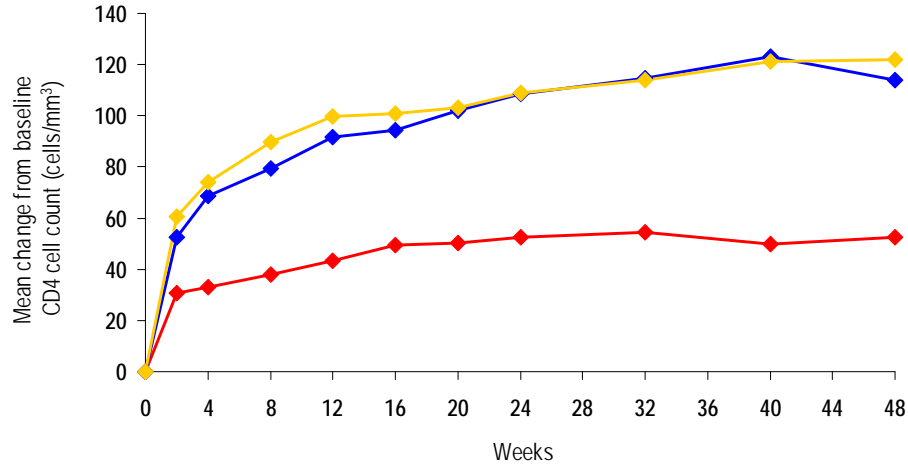


PBO	n=	91	88	82	54	48	39	35	32	32	30	29	29	22
MVC QD	n=	182	180	169	150	143	132	127	124	122	117	115	109	83
MVC BID	n=	191	182	175	157	149	139	139	133	132	131	131	128	101

(C) CD4 Cell Count ‡

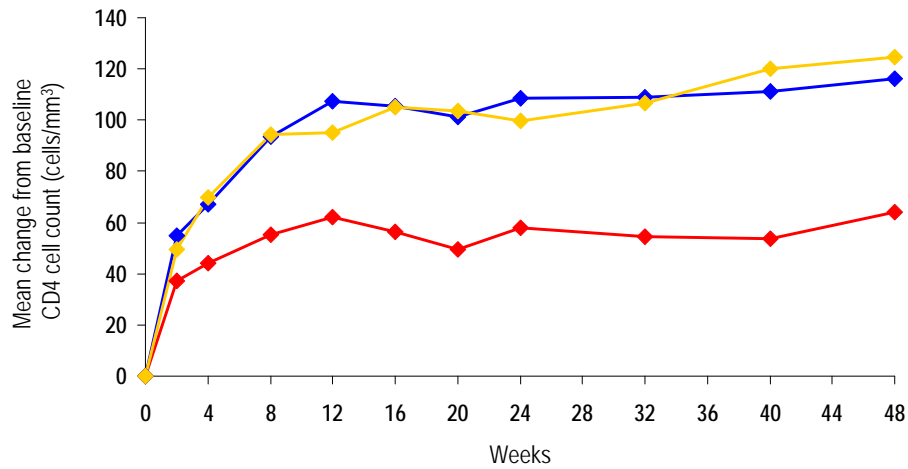
— Placebo plus OBT — Maraviroc, once daily plus OBT — Maraviroc, twice daily plus OBT

MOTIVATE 1



PBO	n=	105	115	116	116	116	116	116	116	116
MVC QD	n=	203	223	226	227	227	227	227	227	227
MVC BID	n=	212	228	232	233	233	233	233	233	233

MOTIVATE 2



PBO	n=	81	90	90	90	90	90	90	90	90
MVC QD	n=	159	176	179	180	180	180	180	180	180
MVC BID	n=	174	184	185	185	185	185	185	185	185

OBT, optimized background therapy; QD, once daily; BID, twice daily; PBO, placebo; MVC, maraviroc

* All patients who received at least one dose of study treatment.

† HIV-1 RNA value defined as the baseline level if missing or if patient discontinued before 48 weeks.

‡ Last observation carried forward