

Supplementary Appendix 2

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

Supplement to: Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008;359:339-54.

SUPPLEMENTARY METHODS

Detailed Safety Analysis Plan

Frequencies of adverse events were not adjusted for duration of follow-up. Differences in the proportions of patients with adverse experiences in each treatment group during the double-blind phases of the combined studies were to be compared using the two-tailed Fisher exact test only for the following categories: (1) at least one clinical adverse event; (2) drug-related clinical adverse event; (3) serious clinical adverse event; (4) serious and drug-related clinical adverse event; (5) discontinued study therapy due to a clinical adverse event. Adjustments were not made for multiplicity.

The percentages of patients with specific adverse experiences by organ system were tabulated by treatment group. No formal hypothesis testing was prespecified for individual adverse experiences. Differences in the proportions of patients with adverse experiences in each treatment group during the double-blind phases of the combined studies were compared by organ system using asymptotic two-sided 95% confidence intervals calculated by the method of Miettinen and Nurminen to indicate the precision of the study sample estimates of treatment differences for adverse experiences for each organ system. Exclusion of zero from the confidence interval does not necessarily correspond with statistical significance at $\alpha = 0.05$ computed from the Fisher exact test.

Table A1. Details of Clinical AIDS-Defining Events during the Double-Blind Phases of the Combined BENCHMRK Studies

Study	Treatment Group	AIDS-Defining Event [†]	Study Day of Initial Diagnosis	CD4 Count at Diagnosis [‡] (cells/mm ³)	CD4 Count at Baseline (cells/mm ³)	Δ CD4 Count: Diagnosis – Baseline (cells/mm ³)
BENCHMRK-1	Raltegravir	Candidiasis, esophageal	169	104	347	-243
	Raltegravir	Lymphoma, immunoblastic; Candidiasis, esophageal	90	139	7	132
	Raltegravir	Encephalopathy, HIV-related	62	125	10	115
	Raltegravir	Kaposi's sarcoma	29	325	6	319
	Raltegravir	Candidiasis, esophageal	162	449	405	44
	Raltegravir	<i>Mycobacterium avium</i> complex (extrapulmonary); Lymphoma, immunoblastic	66	5	3	2
	Raltegravir	Kaposi's sarcoma; Herpes simplex: chronic ulcer(s) (greater than 1 month's duration)	110	12	9	3
	Raltegravir	Candidiasis, esophageal	63	4	2	2
	Raltegravir	Cryptococcal meningitis	307	183	31	152
	Raltegravir	Cryptococcal meningitis	76	182	12	170
	Raltegravir	Herpes simplex: chronic ulcer(s) (greater than 1 month's duration)	134	44	2	42

Placebo	Candidiasis, esophageal	202	26	8	18
Placebo	Candidiasis, esophageal*	9	6	7	-1
Placebo	Cytomegalovirus colitis; Candidiasis, esophageal	120	9	12	-3
Placebo	Candidiasis, esophageal	117	8	5	3
Placebo	Candidiasis, esophageal; Pneumonia, recurrent (other than <i>Mycobacterium avium</i> complex or <i>Pneumocystis carinii</i>)	19	41	22	19

BENCHMRK-2	Raltegravir	Lymphoma, immunoblastic	64	33	46	-13
	Raltegravir	Cytomegalovirus colitis; Microsporidiosis	52	9	6	3
	Raltegravir	Herpes simplex: esophagitis [§]	63	46	198	-152
	Raltegravir	Cryptococcal meningitis [§]	9	43	3	40
	Raltegravir	Pneumonia, recurrent (other than <i>Mycobacterium avium</i> complex or <i>Pneumocystis carinii</i>); Candidiasis, esophageal	48	4	3	1
	Raltegravir	Cytomegalovirus retinitis	43	11	1	10
	Placebo	Cytomegalovirus retinitis; Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)	118	9	3	6

Placebo	Candidiasis, esophageal	75	17	14	3
Placebo	<i>Mycobacterium avium</i> complex (extrapulmonary) [§] ; Lymphoma, immunoblastic	117	180	63	117
Placebo	<i>Salmonella</i> septicemia, recurrent	105	3	4	-1
Placebo	Cryptosporidiosis, chronic intestinal (greater than 1 month's duration); Cytomegalovirus retinitis	66	5	13	-8
Placebo	Candidiasis, esophageal	15	43	44	-1

[†] Definitions of AIDS defining events were modeled on 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults and the list of AIDS-Defining Conditions used in AIDS Clinical Trials Group Protocol A5175.

[‡] The CD4 cell counts tabulated here were the available counts closest in time (but within ± 4 weeks) to diagnosis of the initial AIDS-defining event. If two counts were equidistant from the day of diagnosis, the later value was used.

* This patient also had extrapulmonary infection with *Mycobacterium avium* complex prior to entering the study.

[§] Indicates that an investigator considered immune reconstitution syndrome near the time of diagnosis of an AIDS-defining event. Information regarding possible immune reconstitution syndrome was not actively solicited.

Table A2. Proportion Of Patients With Serious Clinical Adverse Events During The Double-Blind Phases Of The Combined BENCHMRK Studies Regardless Of Incidence Or Causality

	Raltegravir (N = 462)		Placebo (N = 237)		Difference [Raltegravir - Placebo]	
Weeks of follow-up, median (range)	57.4	(3.0, 72.0)	37.6	(5.6, 72.9)		
	n	(%)	n	(%)	% Difference	(95% C.I.)
Patients With One Or More Serious Adverse Events	82	(17.7)	45	(19.0)	-1.2	(-7.6, 4.6)
Blood And Lymphatic System Disorders	4	(0.9)	4	(1.7)	-0.8	(-3.5, 0.8)
Anaemia	3	(0.6)	0	(0.0)		
Febrile Neutropenia	0	(0.0)	1	(0.4)		
Haemolytic Anaemia	1	(0.2)	0	(0.0)		
Leukopenia	0	(0.0)	1	(0.4)		
Neutropenia	1	(0.2)	2	(0.8)		
Cardiac Disorders	9	(1.9)	4	(1.7)	0.3	(-2.5, 2.3)
Acute Coronary Syndrome	2	(0.4)	0	(0.0)		
Angina Pectoris	1	(0.2)	0	(0.0)		
Cardiac Failure Congestive	1	(0.2)	0	(0.0)		
Cardio-Respiratory Arrest	1	(0.2)	0	(0.0)		
Coronary Artery Disease	1	(0.2)	1	(0.4)		
Left Ventricular Dysfunction	0	(0.0)	1	(0.4)		
Mitral Valve Incompetence	0	(0.0)	1	(0.4)		
Myocardial Infarction	2	(0.4)	2	(0.8)		
Pericarditis	1	(0.2)	0	(0.0)		
Ventricular Tachycardia	1	(0.2)	0	(0.0)		
Ear And Labyrinth Disorders	0	(0.0)	2	(0.8)	-0.8	(-3.0, 0.0)
Hypoacusis	0	(0.0)	1	(0.4)		
Vertigo	0	(0.0)	1	(0.4)		
Endocrine Disorders	1	(0.2)	0	(0.0)	0.2	(-1.4, 1.2)
Hyperthyroidism	1	(0.2)	0	(0.0)		
Eye Disorders	1	(0.2)	1	(0.4)	-0.2	(-2.2, 0.8)
Endophthalmitis	1	(0.2)	0	(0.0)		
Uveitis	0	(0.0)	1	(0.4)		
Gastrointestinal Disorders	12	(2.6)	4	(1.7)	0.9	(-1.9, 3.1)
Abdominal Pain	2	(0.4)	0	(0.0)		
Anal Fistula	0	(0.0)	1	(0.4)		
Ascites	1	(0.2)	0	(0.0)		
Diarrhoea	2	(0.4)	0	(0.0)		
Gastritis	1	(0.2)	0	(0.0)		
Hernial Eventration	1	(0.2)	0	(0.0)		
Ileitis	0	(0.0)	1	(0.4)		
Lower Gastrointestinal Haemorrhage	1	(0.2)	0	(0.0)		
Nausea	1	(0.2)	0	(0.0)		
Pancreatitis	0	(0.0)	1	(0.4)		

	Raltegravir (N = 462)		Placebo (N = 237)		Difference [Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference	(95% C.I.)
Rectal Haemorrhage	1	(0.2)	0	(0.0)		
Rectal Stenosis	0	(0.0)	1	(0.4)		
Small Intestinal Obstruction	1	(0.2)	0	(0.0)		
Upper Gastrointestinal Haemorrhage	1	(0.2)	0	(0.0)		
Varices Oesophageal	1	(0.2)	0	(0.0)		
Vomiting	1	(0.2)	0	(0.0)		
General Disorders And Administration Site Conditions	7	(1.5)	5	(2.1)	-0.6	(-3.4, 1.4)
Asthenia	0	(0.0)	2	(0.8)		
Death	1	(0.2)	0	(0.0)		
Malaise	2	(0.4)	0	(0.0)		
Multi-Organ Failure	1	(0.2)	0	(0.0)		
Oedema Peripheral	1	(0.2)	0	(0.0)		
Pyrexia	3	(0.6)	4	(1.7)		
Hepatobiliary Disorders	3	(0.6)	2	(0.8)	-0.2	(-2.4, 1.2)
Cholangitis	1	(0.2)	0	(0.0)		
Gallbladder Disorder	0	(0.0)	1	(0.4)		
Hepatitis	1	(0.2)	0	(0.0)		
Hepatitis Toxic	0	(0.0)	1	(0.4)		
Portal Hypertension	1	(0.2)	0	(0.0)		
Immune System Disorders	4	(0.9)	0	(0.0)	0.9	(-0.7, 2.2)
Drug Hypersensitivity	1	(0.2)	0	(0.0)		
Hypersensitivity	2	(0.4)	0	(0.0)		
Immune Reconstitution Syndrome [§]	2	(0.4)	0	(0.0)		
Infections And Infestations	38	(8.2)	20	(8.4)	-0.2	(-5.0, 3.9)
AIDS Dementia Complex	0	(0.0)	1	(0.4)		
Abscess Bacterial	1	(0.2)	0	(0.0)		
Acinetobacter Bacteraemia	1	(0.2)	0	(0.0)		
Appendicitis	1	(0.2)	1	(0.4)		
Aspergillosis	1	(0.2)	0	(0.0)		
Atypical Mycobacterial Lymphadenitis	0	(0.0)	1	(0.4)		
Bronchitis	1	(0.2)	0	(0.0)		
Bronchopneumonia	2	(0.4)	0	(0.0)		
Cellulitis	3	(0.6)	0	(0.0)		
Choriomeningitis Lymphocytic	2	(0.4)	0	(0.0)		
Clostridium Difficile Colitis	0	(0.0)	1	(0.4)		
Cryptosporidiosis Infection	0	(0.0)	1	(0.4)		
Cytomegalovirus Chorioretinitis	0	(0.0)	2	(0.8)		
Cytomegalovirus Colitis	1	(0.2)	1	(0.4)		
Cytomegalovirus Hepatitis	1	(0.2)	0	(0.0)		
Cytomegalovirus Infection	1	(0.2)	0	(0.0)		
End Stage AIDS	0	(0.0)	1	(0.4)		
Endocarditis	0	(0.0)	1	(0.4)		

	Raltegravir (N = 462)		Placebo (N = 237)		Difference [Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference	(95% C.I.)
Erythema Infectiosum	0	(0.0)	1	(0.4)		
Gastroenteritis	0	(0.0)	1	(0.4)		
Gastroenteritis Salmonella	0	(0.0)	1	(0.4)		
Genital Herpes	2	(0.4)	0	(0.0)		
Giardiasis	0	(0.0)	1	(0.4)		
HIV Infection	1	(0.2)	0	(0.0)		
Herpes Zoster Disseminated	1	(0.2)	0	(0.0)		
Infection	1	(0.2)	0	(0.0)		
Influenza	0	(0.0)	1	(0.2)		
Meningitis Cryptococcal	3	(0.6)	0	(0.0)		
Mycobacterial Infection	1	(0.2)	0	(0.0)		
Mycobacterium Avium Complex	0	(0.0)	2	(0.8)		
Oesophageal Candidiasis	1	(0.2)	3	(1.3)		
Oral Candidiasis	0	(0.0)	1	(0.4)		
Osteomyelitis	1	(0.2)	0	(0.0)		
Otitis Media	1	(0.2)	0	(0.0)		
Pneumonia	9	(1.9)	5	(2.1)		
Pneumonia Pneumococcal	1	(0.2)	0	(0.0)		
Pseudomonal Sepsis	0	(0.0)	1	(0.4)		
Pyelonephritis	1	(0.2)	0	(0.0)		
Respiratory Tract Infection	1	(0.2)	0	(0.0)		
Retroviral Infection	1	(0.2)	0	(0.0)		
Salmonella Bacteraemia	0	(0.0)	1	(0.4)		
Sepsis	0	(0.0)	1	(0.4)		
Septic Shock	2	(0.4)	1	(0.4)		
Sinusitis	2	(0.4)	0	(0.0)		
Staphylococcal Bacteraemia	1	(0.2)	0	(0.0)		
Subcutaneous Abscess	1	(0.2)	0	(0.0)		
Tuberculosis	1	(0.2)	0	(0.0)		
Urosepsis	0	(0.0)	2	(0.8)		
Viral Infection	1	(0.2)	0	(0.0)		
Injury, Poisoning And Procedural Complications	11	(2.4)	4	(1.7)	0.7	(-2.1, 2.8)
Accidental Overdose	1	(0.2)	0	(0.0)		
Foot Fracture	1	(0.2)	0	(0.0)		
Hip Fracture	0	(0.0)	2	(0.8)		
Humerus Fracture	1	(0.2)	0	(0.0)		
Incisional Hernia	1	(0.2)	0	(0.0)		
Intentional Overdose	1	(0.2)	1	(0.4)		
Lower Limb Fracture	2	(0.4)	0	(0.0)		
Overdose	1	(0.2)	0	(0.0)		
Post Procedural Haematuria	1	(0.2)	0	(0.0)		
Post Procedural Haemorrhage	1	(0.2)	0	(0.0)		
Spinal Fracture	1	(0.2)	0	(0.0)		

	Raltegravir (N = 462)		Placebo (N = 237)		Difference [Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference	(95% C.I.)
Thoracic Vertebral Fracture	0	(0.0)	1	(0.4)		
Investigations	1	(0.2)	0	(0.0)	0.2	(-1.4, 1.2)
Weight Decreased	1	(0.2)	0	(0.0)		
Metabolism And Nutrition Disorders	5	(1.1)	4	(1.7)	-0.6	(-3.3, 1.2)
Cachexia	1	(0.2)	0	(0.0)		
Dehydration	3	(0.6)	1	(0.4)		
Diabetes Mellitus	1	(0.2)	0	(0.0)		
Failure To Thrive	0	(0.0)	1	(0.4)		
Hyperglycaemia	0	(0.0)	1	(0.4)		
Hypovolaemia	0	(0.0)	1	(0.4)		
Malnutrition	0	(0.0)	1	(0.4)		
Obesity	0	(0.0)	1	(0.4)		
Musculoskeletal And Connective Tissue Disorders	4	(0.9)	2	(0.8)	0.0	(-2.2, 1.5)
Bone Pain	1	(0.2)	0	(0.0)		
Intervertebral Disc Protrusion	0	(0.0)	1	(0.4)		
Musculoskeletal Pain	1	(0.2)	0	(0.0)		
Osteonecrosis	2	(0.4)	0	(0.0)		
Osteoporotic Fracture	0	(0.0)	1	(0.4)		
Neoplasms Benign, Malignant And Unspecified (Including Cysts/Polyps)	16	(3.5)	4	(1.7)	1.8	(-1.1, 4.2)
Anal Cancer	1	(0.2)	1	(0.4)		
Anal Cancer Stage 0	1	(0.2)	0	(0.0)		
B-Cell Lymphoma	1	(0.2)	0	(0.0)		
Basal Cell Carcinoma	1	(0.2)	1	(0.4)		
Bowen's Disease	1	(0.2)	0	(0.0)		
Hepatic Neoplasm Malignant	1	(0.2)	0	(0.0)		
Kaposi's Sarcoma AIDS Related	2	(0.4)	0	(0.0)		
Lymphoma	1	(0.2)	1	(0.4)		
Metastatic Squamous Cell Carcinoma	1	(0.2)	0	(0.0)		
Rectal Cancer	1	(0.2)	0	(0.0)		
Rectal Cancer Stage 0	1	(0.2)	0	(0.0)		
Squamous Cell Carcinoma	4	(0.9)	1	(0.4)		
T-Cell Lymphoma	1	(0.2)	0	(0.0)		
Nervous System Disorders	6	(1.3)	5	(2.1)	-0.8	(-3.6, 1.1)
Cerebral Infarction	0	(0.0)	1	(0.4)		
Convulsion	1	(0.2)	1	(0.4)		
Encephalitis	1	(0.2)	0	(0.0)		
Epilepsy	0	(0.0)	1	(0.4)		
Migraine	1	(0.2)	1	(0.4)		
Neuralgia	1	(0.2)	0	(0.0)		
Poor Quality Sleep	0	(0.0)	1	(0.4)		
Presyncope	1	(0.2)	0	(0.0)		
Psychomotor Hyperactivity	0	(0.0)	1	(0.4)		
Syncope	1	(0.2)	0	(0.0)		

	Raltegravir (N = 462)		Placebo (N = 237)		Difference [Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference	(95% C.I.)
Psychiatric Disorders	3	(0.6)	3	(1.3)	-0.6	(-3.1, 0.9)
Depression	2	(0.4)	2	(0.8)		
Mental Status Changes	1	(0.2)	1	(0.4)		
Panic Attack	0	(0.0)	1	(0.4)		
Renal And Urinary Disorders	6	(1.3)	4	(1.7)	-0.4	(-3.1, 1.4)
Focal Glomerulosclerosis	1	(0.2)	0	(0.0)		
Nephrolithiasis	1	(0.2)	1	(0.4)		
Nephropathy	0	(0.0)	1	(0.4)		
Nephropathy Toxic	1	(0.2)	0	(0.0)		
Nephrotic Syndrome	1	(0.2)	0	(0.0)		
Proteinuria	1	(0.2)	0	(0.0)		
Renal Failure	1	(0.2)	1	(0.4)		
Renal Failure Acute	0	(0.0)	1	(0.4)		
Renal Failure Chronic	1	(0.2)	0	(0.0)		
Renal Tubular Necrosis	1	(0.2)	0	(0.0)		
Reproductive System And Breast Disorders	3	(0.6)	2	(0.8)	-0.2	(-2.4, 1.2)
Benign Prostatic Hyperplasia	1	(0.2)	0	(0.0)		
Gynaecomastia	0	(0.0)	1	(0.4)		
Oedema Genital	0	(0.0)	1	(0.4)		
Prostatitis	2	(0.4)	0	(0.0)		
Respiratory, Thoracic And Mediastinal Disorders	4	(0.9)	2	(0.8)	0.0	(-2.2, 1.5)
Asthma	2	(0.4)	0	(0.0)		
Pulmonary Hypertension	0	(0.0)	1	(0.4)		
Respiratory Distress	1	(0.2)	0	(0.0)		
Respiratory Failure	1	(0.2)	1	(0.4)		
Vascular Disorders	2	(0.4)	3	(1.3)	-0.8	(-3.3, 0.5)
Deep Vein Thrombosis	1	(0.2)	0	(0.0)		
Hypotension	0	(0.0)	1	(0.4)		
Shock	1	(0.2)	0	(0.0)		
Varicophlebitis	0	(0.0)	1	(0.4)		
Venous Thrombosis	0	(0.0)	1	(0.4)		

Adverse event terms are from the Medical Dictionary for Regulatory Activities (MedDRA version 10.1).

Frequencies of adverse events were not adjusted for duration of follow-up. A patient is counted only once within a given organ system category, but may be tabulated more than once in different subcategories; a patient may also appear in more than one organ system category.

N = Number of patients in each treatment group.

n (%) = number (percent) of patients in each subcategory.

§ Indicates that the investigator reported immune reconstitution syndrome as an adverse event. Information regarding possible immune reconstitution syndrome was not actively solicited. Not all reports of immune reconstitution syndrome were recorded as adverse events.

Table A3. Proportion Of Patients With Specific Clinical Adverse Events Of Any Intensity Or Causality During The Double-Blind Phases Of The Combined BENCHMRK Studies With An Incidence $\geq 2\%$ In Either Treatment Group

	Raltegravir Group (N = 462)		Placebo Group (N = 237)		Difference [Raltegravir - Placebo]	
Weeks of follow-up, median (range)	57.4	(3.0, 72.0)	37.6	(5.6, 72.9)		
	n	(%)	n	(%)	% Difference (95% C.I.)	
Patients With One Or More Adverse Events	417	(90.3)	209	(88.2)	2.1	(-2.6, 7.4)
Blood And Lymphatic System Disorders	39	(8.4)	21	(8.9)	-0.4	(-5.3, 3.8)
Anaemia	14	(3.0)	9	(3.8)		
Lymphadenopathy	17	(3.7)	7	(3.0)		
Neutropenia	6	(1.3)	5	(2.1)		
Cardiac Disorders	17	(3.7)	9	(3.8)	-0.1	(-3.7, 2.7)
Ear And Labyrinth Disorders	13	(2.8)	5	(2.1)	0.7	(-2.2, 3.0)
Eye Disorders	24	(5.2)	15	(6.3)	-1.1	(-5.3, 2.3)
Conjunctivitis	10	(2.2)	1	(0.4)		
Gastrointestinal Disorders	204	(44.2)	110	(46.4)	-2.3	(-10.1, 5.5)
Abdominal Distension	13	(2.8)	7	(3.0)		
Abdominal Pain	27	(5.8)	10	(4.2)		
Abdominal Pain Upper	13	(2.8)	10	(4.2)		
Constipation	14	(3.0)	1	(0.4)		
Diarrhoea	85	(18.4)	50	(21.1)		
Flatulence	16	(3.5)	7	(3.0)		
Nausea	53	(11.5)	34	(14.3)		
Vomiting	34	(7.4)	22	(9.3)		
General Disorders And Administration Site Conditions	168	(36.4)	85	(35.9)	0.5	(-7.1, 7.9)
Asthenia	15	(3.2)	9	(3.8)		
Fatigue	43	(9.3)	11	(4.6)		
Injection Site Pain	10	(2.2)	3	(1.3)		
Injection Site Reaction	46	(10.0)	23	(9.7)		
Oedema Peripheral	9	(1.9)	7	(3.0)		
Pyrexia	31	(6.7)	30	(12.7)		
Hepatobiliary Disorders	13	(2.8)	8	(3.4)	-0.6	(-3.9, 2.0)
Immune System Disorders	14	(3.0)	5	(2.1)	0.9	(-2.1, 3.3)
Infections And Infestations	269	(58.2)	132	(55.7)	2.5	(-5.2, 10.3)
Anogenital Warts	11	(2.4)	2	(0.8)		
Bronchitis	34	(7.4)	11	(4.6)		
Cellulitis	11	(2.4)	4	(1.7)		
Folliculitis	12	(2.6)	2	(0.8)		
Gastroenteritis	15	(3.2)	5	(2.1)		
Genital Herpes	10	(2.2)	6	(2.5)		
Herpes Simplex	10	(2.2)	3	(1.3)		
Herpes Zoster	28	(6.1)	3	(1.3)		

	Raltegravir Group		Placebo Group		Difference	
	(N = 462)		(N = 237)		[Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference (95% C.I.)	
Influenza	23	(5.0)	9	(3.8)		
Nasopharyngitis	37	(8.0)	14	(5.9)		
Oesophageal Candidiasis	3	(0.6)	6	(2.5)		
Oral Candidiasis	7	(1.5)	19	(8.0)		
Pneumonia	16	(3.5)	9	(3.8)		
Respiratory Tract Infection	12	(2.6)	1	(0.4)		
Sinusitis	18	(3.9)	8	(3.4)		
Tooth Infection	2	(0.4)	5	(2.1)		
Upper Respiratory Tract Infection	37	(8.0)	17	(7.2)		
Urinary Tract Infection	7	(1.5)	8	(3.4)		
Injury, Poisoning And Procedural Complications	50	(10.8)	22	(9.3)	1.5	(-3.5, 6.0)
Investigations	23	(5.0)	17	(7.2)	-2.2	(-6.6, 1.4)
Weight Decreased	10	(2.2)	7	(3.0)		
Metabolism And Nutrition Disorders	52	(11.3)	26	(11.0)	0.3	(-5.0, 5.0)
Anorexia	10	(2.2)	6	(2.5)		
Musculoskeletal And Connective Tissue Disorders	94	(20.3)	37	(15.6)	4.7	(-1.5, 10.4)
Arthralgia	18	(3.9)	7	(3.0)		
Back Pain	17	(3.7)	8	(3.4)		
Muscle Spasms	8	(1.7)	6	(2.5)		
Myalgia	10	(2.2)	7	(3.0)		
Pain In Extremity	20	(4.3)	7	(3.0)		
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	41	(8.9)	13	(5.5)	3.4	(-0.9, 7.2)
Skin Papilloma	18	(3.9)	8	(3.4)		
Nervous System Disorders	120	(26.0)	59	(24.9)	1.1	(-5.9, 7.7)
Dizziness	21	(4.5)	6	(2.5)		
Headache	47	(10.2)	30	(12.7)		
Paraesthesia	6	(1.3)	5	(2.1)		
Psychiatric Disorders	62	(13.4)	34	(14.3)	-0.9	(-6.7, 4.3)
Anxiety	10	(2.2)	6	(2.5)		
Depression	13	(2.8)	9	(3.8)		
Insomnia	22	(4.8)	11	(4.6)		
Renal And Urinary Disorders	31	(6.7)	14	(5.9)	0.8	(-3.4, 4.4)
Reproductive System And Breast Disorders	31	(6.7)	9	(3.8)	2.9	(-0.8, 6.2)
Respiratory, Thoracic And Mediastinal Disorders	69	(14.9)	37	(15.6)	-0.7	(-6.6, 4.8)
Cough	25	(5.4)	8	(3.4)		
Pharyngolaryngeal Pain	11	(2.4)	9	(3.8)		
Sinus Congestion	3	(0.6)	5	(2.1)		
Skin And Subcutaneous Tissue Disorders	134	(29.0)	53	(22.4)	6.6	(-0.3, 13.2)
Eczema	4	(0.9)	7	(3.0)		
Night Sweats	13	(2.8)	5	(2.1)		

	Raltegravir Group		Placebo Group		Difference	
	(N = 462)		(N = 237)		[Raltegravir - Placebo]	
	n	(%)	n	(%)	% Difference (95% C.I.)	
Pruritus	14	(3.0)	5	(2.1)		
Rash	29	(6.3)	6	(2.5)		
Vascular Disorders	27	(5.8)	13	(5.5)	0.4	(-3.7, 3.8)
Hypertension	15	(3.2)	5	(2.1)		

Adverse event terms are from the Medical Dictionary for Regulatory Activities (MedDRA version 10.1). Frequencies of adverse events were not adjusted for duration of follow-up. A patient is counted only once within a given organ system category, but may be tabulated more than once in different subcategories; a patient may also appear in more than one organ system category.

N = Number of patients in each treatment group.

n (%) = number (percent) of patients in each subcategory.

Table A4. Proportion Of Patients With Laboratory Abnormalities Exceeding Predefined Limits Of Change (PDLC) During The Double-Blind Phases Of The Combined BENCHMRK Studies

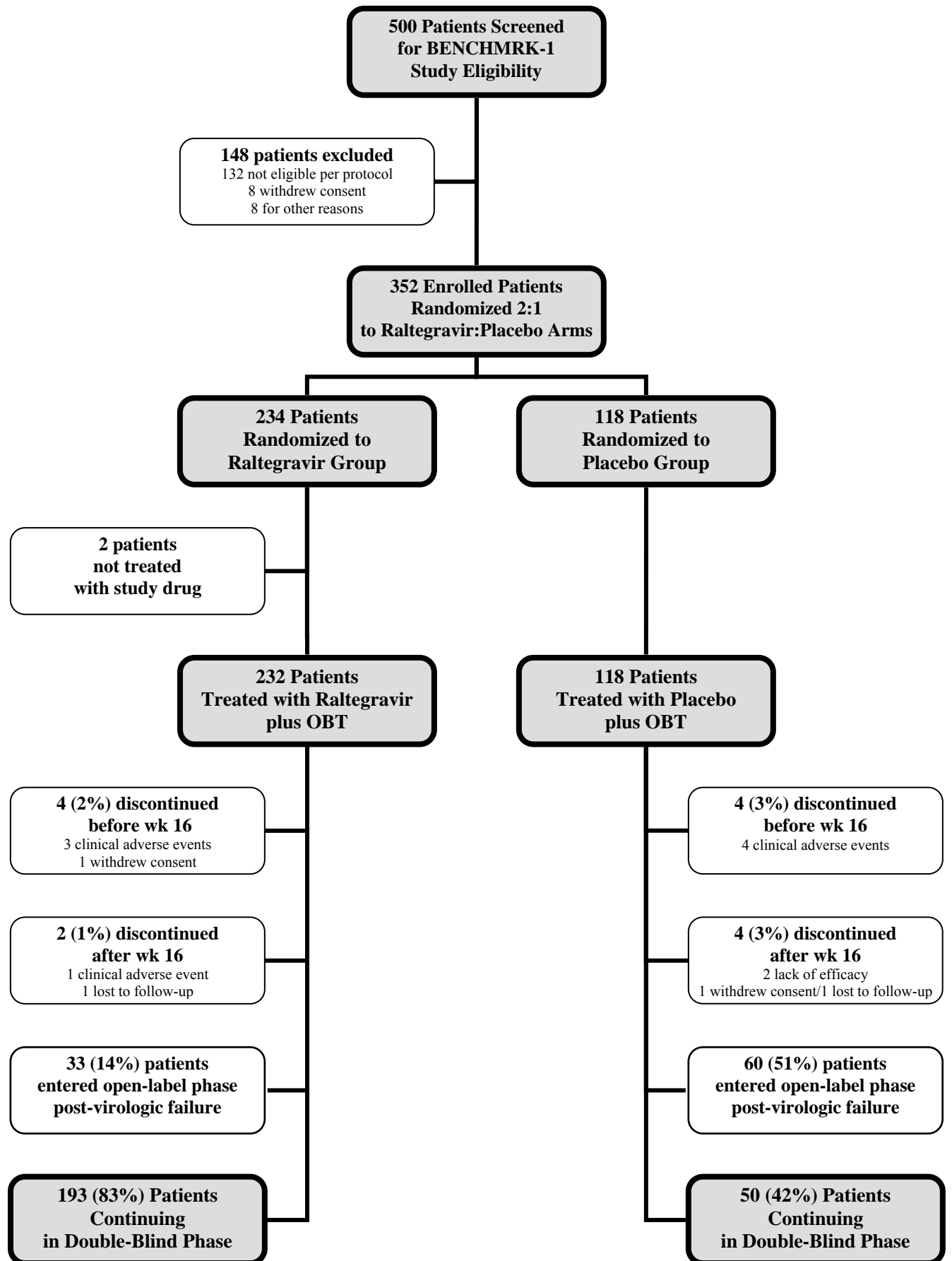
Laboratory Test (Unit)	PDLC Criteria	Grade	Raltegravir (N=462) n/m (%)	Placebo (N=237) n/m (%)	Difference [Raltegravir - Placebo] % Difference (95% C.I.)
hematology laboratory tests					
absolute neutrophil count (10 ³ /microL)	0.75 - 0.999	Grade 2	17/462 (3.7)	18/237 (7.6)	-4.0 (-9.2, 0.5)
	0.50 - 0.749	Grade 3	14/462 (3.0)	8/237 (3.4)	
	<0.50	Grade 4	5/462 (1.1)	2/237 (0.8)	
	<1.00	Gr 2 - 4	36/462 (7.8)	28/237 (11.8)	
hemoglobin (gm/dL)	7.5 - 8.4	Grade 2	5/462 (1.1)	6/237 (2.5)	-0.8 (-4.0, 1.6)
	6.5 - 7.4	Grade 3	4/462 (0.9)	1/237 (0.4)	
	< 6.5	Grade 4	1/462 (0.2)	0/237 (0.0)	
	< 8.5	Gr 2 - 4	10/462 (2.2)	7/237 (3.0)	
platelet count (10 ³ /microL)	50 - 99.999	Grade 2	19/462 (4.1)	15/237 (6.3)	-1.5 (-5.9, 2.1)
	25 - 49.999	Grade 3	3/462 (0.6)	1/237 (0.4)	
	<25	Grade 4	4/462 (0.9)	1/237 (0.4)	
	<100	Gr 2 - 4	26/462 (5.6)	17/237 (7.2)	
blood chemistry tests					
fasting(non-random) serum LDL-C (mg/dL)	160 - 189	Grade 2	46/436 (10.6)	12/218 (5.5)	6.2 (0.6, 11.2)
	≥190	Grade 3	23/436 (5.3)	9/218 (4.1)	
	≥160	Gr 2 - 3	69/436 (15.8)	21/218 (9.6)	
fasting(non-random) serum cholesterol (mg/dL)	240 - 300	Grade 2	85/462 (18.4)	34/237 (14.3)	7.4 (0.8, 13.6)
	>300	Grade 3	37/462 (8.0)	11/237 (4.6)	
	≥ 240	Gr 2 - 3	122/462 (26.4)	45/237 (19.0)	

Laboratory Test (Unit)	PDLC Criteria	Grade	Raltegravir (N=462) n/m (%)	Placebo (N=237) n/m (%)	Difference [Raltegravir - Placebo] % Difference (95% C.I.)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	28/462 (6.1)	25/237 (10.5)	-1.1 (-7.1, 4.3)
	751 - 1200	Grade 3	24/462 (5.2)	7/237 (3.0)	
	>1200	Grade 4	15/462 (3.2)	5/237 (2.1)	
	> 500	Gr 2 - 4	67/462 (14.5)	37/237 (15.6)	
fasting(non-random) serum glucose test (mg/dL)	126 - 250	Grade 2	47/462 (10.2)	17/237 (7.2)	3.0 (-2.0, 7.5)
	251 - 500	Grade 3	8/462 (1.7)	4/237 (1.7)	
	>500	Grade 4	0/462 (0.0)	0/237 (0.0)	
	>125	Gr 2 - 4	55/462 (11.9)	21/237 (8.9)	
total serum bilirubin (mg/dL)	1.6 - 2.5 x ULN	Grade 2	26/462 (5.6)	10/237 (4.2)	2.6 (-2.0, 6.6)
	2.6 - 5.0 x ULN	Grade 3	13/462 (2.8)	6/237 (2.5)	
	>5.0 x ULN	Grade 4	4/462 (0.9)	0/237 (0.0)	
	>1.5 x ULN	Gr 2 - 4	43/462 (9.3)	16/237 (6.8)	
	>2.5 - 5.0 x Baseline [‡]		19/462 (4.1)	9/237 (3.8)	
	>5.0 -10.0 x Baseline [‡]		16/462 (3.5)	7/237 (3.0)	
	>10.0 x Baseline [‡]		10/462 (2.2)	0/237 (0.0)	
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline [‡]		10/462 (2.2)	4/237 (1.7)	
	>5.0 - 10.0 x Baseline [‡]		1/462 (0.2)	4/237 (1.7)	
	>10.0 x Baseline [‡]		5/462 (1.1)	0/237 (0.0)	
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline [‡]		6/462 (1.3)	1/237 (0.4)	
	>5.0 - 10.0 x Baseline [‡]		15/462 (3.2)	6/237 (2.5)	
	>10.0 x Baseline [‡]		12/462 (2.6)	2/237 (0.8)	
serum creatinine (mg/dL)	1.4 - 1.8 x ULN	Grade 2	17/462 (3.7)	7/237 (3.0)	0.8 (-3.0, 3.9)
	1.9 - 3.4 x ULN	Grade 3	5/462 (1.1)	3/237 (1.3)	
	≥3.5 x ULN	Grade 4	1/462 (0.2)	0/237 (0.0)	
	≥1.4 x ULN	Gr 2 - 4	23/462 (5.0)	10/237 (4.2)	
	>2.5 x Baseline [‡]		3/462 (0.6)	0/237 (0.0)	

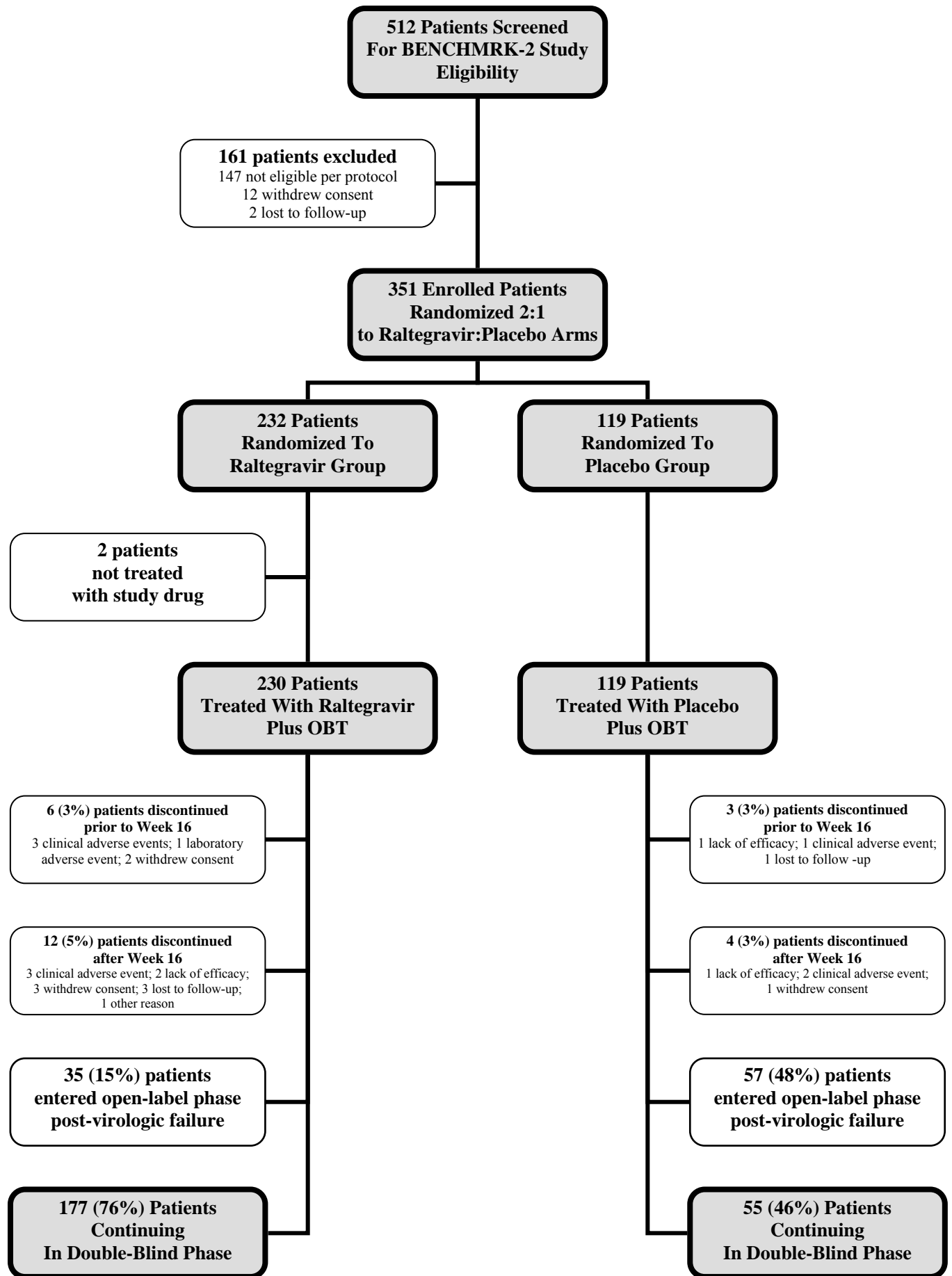
Laboratory Test (Unit)	PDLC Criteria	Grade	Raltegravir (N=462) n/m (%)	Placebo (N=237) n/m (%)	Difference [Raltegravir - Placebo] % Difference (95% C.I.)
serum aspartate aminotransferase (IU/L)	2.6 - 5.0 x ULN	Grade 2	44/462 (9.5)	17/237 (7.2)	1.6 (-3.8, 6.5)
	5.1 - 10.0 x ULN	Grade 3	14/462 (3.0)	7/237 (3.0)	
	>10.0 x ULN	Grade 4	2/462 (0.4)	3/237 (1.3)	
	>2.5 x ULN	Gr 2 - 4	60/462 (13.0)	27/237 (11.4)	
	>2.5 - 5.0 x Baseline [‡]		30/462 (6.5)	12/237 (5.1)	
	>5.0 x Baseline [‡]		14/462 (3.0)	12/237 (5.1)	
serum alanine aminotransferase (IU/L)	2.6 - 5.0 x ULN	Grade 2	36/462 (7.8)	20/237 (8.4)	0.3 (-5.1, 5.2)
	5.1 - 10.0 x ULN	Grade 3	16/462 (3.5)	4/237 (1.7)	
	>10.0 x ULN	Grade 4	4/462 (0.9)	4/237 (1.7)	
	>2.5 x ULN	Gr 2 - 4	56/462 (12.1)	28/237 (11.8)	
	>2.5 - 5.0 x Baseline [‡]		39/462 (8.4)	23/237 (9.7)	
	>5.0 x Baseline [‡]		20/462 (4.3)	8/237 (3.4)	
serum alkaline phosphatase (IU/L)	2.6 - 5.0 x ULN	Grade 2	11/462 (2.4)	1/237 (0.4)	1.4 (-1.7, 3.8)
	5.1 - 10.0 x ULN	Grade 3	2/462 (0.4)	3/237 (1.3)	
	>10.0 x ULN	Grade 4	3/462 (0.6)	1/237 (0.4)	
	>2.5 x ULN	Gr 2 - 4	16/462 (3.5)	5/237 (2.1)	
	>2.5 - 5.0 x Baseline [‡]		8/462 (1.7)	2/237 (0.8)	
	>5.0 x Baseline [‡]		2/462 (0.4)	1/237 (0.4)	
serum pancreatic amylase test (IU/L) [§]	1.6 - 2.0 x ULN	Grade 2	8/462 (1.7)	3/237 (1.3)	2.3 (-1.4, 5.5)
	2.1 - 5.0 x ULN	Grade 3	19/462 (4.1)	6/237 (2.5)	
	>5.0 x ULN	Grade 4	1/462 (0.2)	0/237 (0.0)	
	>1.5 x ULN	Gr 2 - 4	28/462 (6.1)	9/237 (3.8)	
serum lipase test (IU/L)	1.6 - 3.0 x ULN	Grade 2	18/462 (3.9)	6/237 (2.5)	1.6 (-1.9, 4.6)
	3.1 - 5.0 x ULN	Grade 3	5/462 (1.1)	2/237 (0.8)	
	>5.0 x ULN	Grade 4	0/462 (0.0)	0/237 (0.0)	
	>1.5 x ULN	Gr 2 - 4	23/462 (5.0)	8/237 (3.4)	

Laboratory Test (Unit)	PDLC Criteria	Grade	Raltegravir (N=462) n/m (%)	Placebo (N=237) n/m (%)	Difference [Raltegravir - Placebo] % Difference (95% C.I.)
serum creatine kinase (IU/L)	6.0 - 9.9 x ULN	Grade 2	11/462 (2.4)	4/237 (1.7)	2.7 (-1.4, 6.3)
	10.0 - 19.9 x ULN	Grade 3	15/462 (3.2)	6/237 (2.5)	
	≥20.0 x ULN	Grade 4	10/462 (2.2)	2/237 (0.8)	
	>6.0 x ULN	Gr 2 - 4	36/462 (7.8)	12/237 (5.1)	
<p>† For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.</p> <p>‡ A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal.</p> <p>§ Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).</p> <p>N = total number of patients randomized in the treatment group.</p> <p>n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.</p> <p>LLN = Lower limit of normal range. ULN = Upper limit of normal range.</p>					

Supplemental Figure 1A. BENCHMRK-1

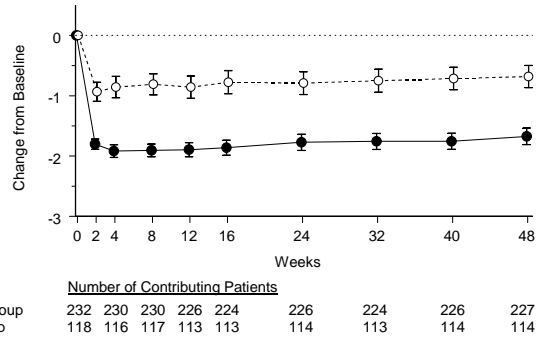


Supplemental Figure 1B. BENCHMRK-2

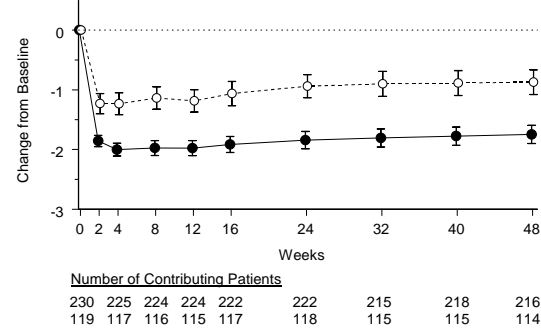


Supplemental Figure 2.

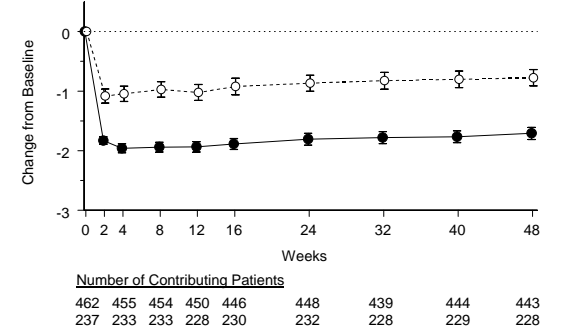
A. BENCHMRK-1



B. BENCHMRK-2



C. Combined BENCHMRK Studies



Mean change in vRNA levels (log₁₀ copies/mL)

Mean change in CD4 counts (cells/mm³)

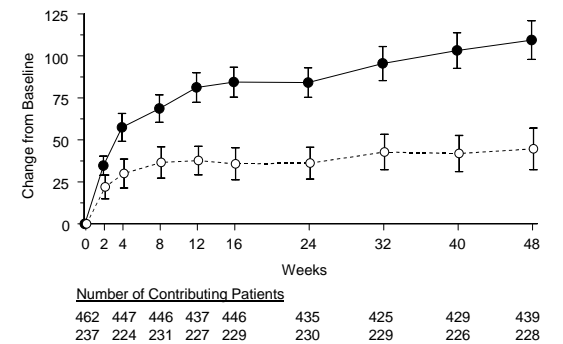
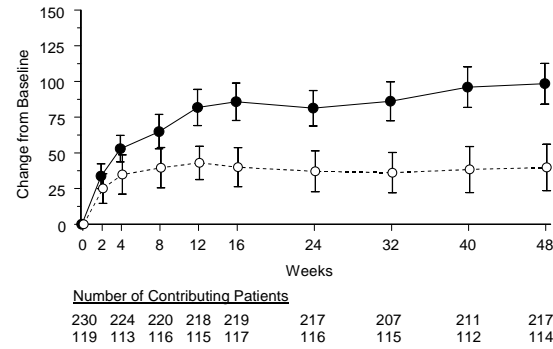
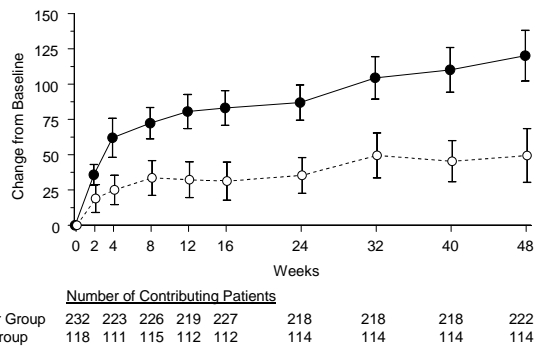


FIGURE LEGENDS

Supplemental Figure 1. Subject accounting for BENCHMRK-1 (A) and BENCHMRK-2 (B)

Data regarding patient disposition are presented as of 3-August-2007 for BENCHMRK-1 and 31-July-2007 for BENCHMRK-2. The time point for the primary efficacy analysis was prespecified by protocol as study Week 16; full 48-week efficacy data are presented in this report. Subsequent to Week 16, patients with virologic failure could opt to remain in the blinded portion of the study, enter an open-label phase and receive raltegravir as part of a new regimen, or withdraw from the study. OBT, optimized background therapy.

Supplemental Figure 2. Change from baseline in vRNA levels and CD4-cell counts over time by treatment group for BENCHMRK-1 (A), BENCHMRK-2 (B), and the combined BENCHMRK studies (C)

The mean change in \log_{10} vRNA copies per mL and CD4-cell counts per mm^3 from baseline are shown using the observed-failure approach, carrying baseline values forward (thereby assigning a value of 0 to change from baseline) for all failures. Vertical brackets represent the 95% confidence intervals.