CROI 2010
17th Conference on Retroviruses
and Opportunistic Infections
February 16-19, 2010
San Francisco, CA
Abstract #Q-125
Poster # 662

Hepatic Safety & Efficacy of Raltegravir in Patients Co-infected with HIV and Hepatitis B (HBV) and/or C (HCV) Virus

Jürgen Rockstroh[1], Hedy Teppler[2], Jing Zhao[2], Peter Sklar[2], Charlotte Harvey[2], Randi Leavitt[2], and Bach-Yen Nguyen[2]

[1]University of Bonn, Bonn-Venusberg, Germany; [2]Merck Research Laboratories, West Point, PA, USA

Bach-Yen T. Nguyen, MD
Merck Research Laboratories
Clinical Research, UG3D-56
PO Box 1000
North Wales, PA 19454
bachyen_nguyen@merck.com

Abstract

Objective: This analysis reports long-term hepatic safety and efficacy data from patients (pts) with HBV and/or HCV co-infection who participated in 3 Phase III studies of raltegravir (RAL).

Methods: Each study was double-blind and randomized. In STARTMRK, treatment-naïve pts received RAL 400 mg bid or efavirenz (EFV) 600 mg qhs, both in combination with tenofovir/emtricitabine (TDF/FTC). In BENCHMRK-1 and -2, highly treatment-experienced pts with multi-drug resistant virus failing other therapies received RAL 400 mg bid or placebo, both in combination with optimized background therapy (OBT). Pts with chronic (but not acute) active HBV and/or HCV co-infection were permitted to enroll, provided that baseline liver function tests did not exceed 5 times the upper limit of normal. HBV infection was defined as + Hepatitis B surface antigen for all studies; HCV infection was defined as + HCV RNA for STARTMRK and as + Hepatitis C antibody for BENCHMRK.

Results: In total, 743 pts received RAL and 519 received comparator across the 3 studies. Hepatitis co-infection was present in 16% (114/699) of treatment-experienced pts (HBV=6 %, HCV=9 %, HBV+HCV=1 %) and in 6% (34/563) of treatment-naïve pts (HBV=4 %, HCV=2 %, HBV+HCV=0.2 %). Selected safety and efficacy results at week 96 are shown for pts with (+) HBV/HCV and those without (-) HBV/HCV co-infection.

	BENCHMRK (treatment-experienced)				STARTMRK (treatment-naïve)			
	RAL + OBT		Placebo + OBT		RAL + TDF/FTC		EFV + TDF/FTC	
	+ HBV/HCV N=77 (PYR=125)	- HBV/HCV N=385 (PYR=584)	+ HBV/HCV N=37 (PYR=33)	- HBV/HCV N=200 (PYR=210)	+ HBV/HCV N=18	- HBV/HCV N=263	+ HBV/HCV N=16	- HBV/HCV N=266
Percent (rate/100 PYR)* with lab abnormalities of Grade 3 or 4 and increased grade from baseline								
AST increase	10.4 (6.4)	3.6 (2.4)	2.8 (3.0)	4.5 (4.3)	11.1	2.3	6.3	2.3
ALT increase	13.0 (8.0)	3.6 (2.4)	8.3 (9.1)	3.0 (2.9)	5.6	1.5	12.5	1.9
Bilirubin increase	3.9 (2.4)	3.6 (2.4)	5.6 (6.1)	2.0 (1.9)	0	0.8	0	0
% with Hepatic AE	2.6	3.9	5.4	4.0	0	3.0	0	0.4
% with HIV RNA <50**	63.1	61.4	15.2	30.6	93.3	89.9	92.3	89.4

* Exposure-adjusted rates per 100 patient-years at risk (PYR) are shown for the BENCHMRK studies, due to longer duration of exposure in the RAL group.
** Observed failure approach.

Conclusion: Grade 3,4 liver enzyme elevations were observed more frequently in HIV/HBV/HCV co-infected patients than in HIV-monoinfected patients, but were not different between the raltegravir and control (OBT or EFV) groups. Overall, raltegravir was efficacious and generally well tolerated to 96 weeks in HIV-infected patients with HBV and/or HCV co-infection.

References

1. ISENTRESS (raltegravir) product information, 2009.
2. Lennox et al. ICAAC 2009 [abstract H-924b].
3. Steigbigel et al. Clin Infect Dis 2010;50:605-612.

Acknowledgements

All patients who participated in the STARTMRK and BENCHMRK-1 & 2 studies.

STARTMRK Investigators: *Australia:* Cooper D; Brazil: Madruga J, Netto E, ZajdenverG R; *Canada:* Baril JG, Kovacs C, Smaill F; *Chile:* Afani A, Beltran C, Perez Godoy J; *Colombia:* Angela M, Arango A, Tamara J, Velez J; *France:* Cotte L, Girard P-M, Pialoux G, Salmon Ceron D, Yazdanpanah, Y; *Germany:* Esser S, Fatkenheuer G, Rockstroh J, Schmidt R, Stellbrink H-J; *India:* Dinaker M, Pazare A, Rajendran J, Srivastava O; *Italy:* Carosi G, Chirianni A, Esposito R, Lazzarin A, Viscoli C; *Mexico:* Andrade J, Quintero Perez N, Reyes G, Sierra J, Torres I; *Peru:* Gotuzzo E, Lama J, Cabello R, C, Salazar R; *Spain:* Portilla Sogorb J, Rivero-Roman A, Santamaria Jauregui J; *Thailand:* Vibhagool A, M anosuthi W, Supparatpinyo K; *United States:* Berger D, DeJesus E, Friel, T, Hicks C, Kozal M, Kumar P, Lennox J, Liporace R, Little S, Morales-Ramirez J, Novak R, Pollard R, Saag M, Santiago S, Schneider S, Steigbigel R, Towner W, Wright D.

BENCHMRK-1 Investigators: *Australia:* Allworth A, Anderson J, Bloch M, Cooper DA, Hoy J, Workman C; *Belgium:* Clumeck N, Colebunders R, Moutschen M; *Denmark:* Gerstoft J, Larsen C, Mathiesen L, Pedersen C; *France:* Delfraissy JF, Dellamonica P, Katlama C, Molina JM, Raffi F, Reynes J, Vittecoq D, Yeni P; *Germany:* Arasteh K, Fatkenheuer G, Jaeger H, Rockstroh J, Stoehr A; *Italy:* Aiuti F, Carosi G, Cauda R, Chiodo F, Di Perri G, Filice G, Galli M, Lazzarin A,Vullo V; *Peru:* Castaneda M, Florez A, Mendo F, Paredes A, Salazar R, Ticona E; *Portugal:* Antunes R, Diniz A, Mansinho K, Saraiva da Cunha J, Sarmento R, Teofilo E, Vera J; *Spain:* Arrizabalaga J, Clotet Sala B, Domingo Pedrol P, Gatell Artigas J, Moreno Guillen S, Soriano Vazquez V; *Switzerland:* Hirschel B, Opravil M; *Taiwan:* Lin H-H, Sheng W-H, Wang J-H; *Thailand:* Sungkanuparph S, Suwanagool S

BENCHMRK-2 Investigators: *Brazil:* Grinsztejn B, Madruga JV, Schechter M; *Canada:* Baril J-G, Loutf, MR, Montaner JS, Tremblay C, Tsoukas CM, Vezina S; *Colombia:* Cortes JA, Mendoza H, Velez J; *Mexico:* Quintero Perez N, Ramos J, Rodriguez E; *Puerto Rico:* Morales-Ramirez JO, Sepulveda GE; *US:* Aberg J, Beatty GW, Benson P, Bolon RK, Bredeek UF, Bruno C, Campbell T, Campo R, Coodley GO, Corales RB, DeJesus E, Eron JJ, Fessel, WJ, Fetchick RJ, Gonzales CJ, Hicks C, Horberg MA, Klein DB, Kozal MJ, Kumar PN, LaMarca A, Lennox JL, Lichtenstein KA, Liporace R, Little SJ, Luetkemeyer A, Mariuz P, Markowitz M, McMahon DK, Perez G, Pierone G, Reichman RC, Rhame F, Shalit P, Short W, Skolnik PR, Steigbigel RT, Tedaldi EM, Ward DJ, Wiznia AA, Wright DP

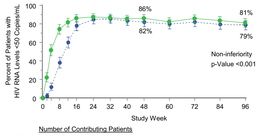
Merck Research Laboratories: C. Harvey, R. Isaacs, B. Jackson, Y. Ke, R. Leavitt, C. Maass, A. Meibohm, B-Y. Nguyen, R. Rhodes, A. Rodgers, P. Sklar, K. Strohmaier, H. Teppler, H. Wan, J. Zhao

Background

- Raltegravir (RAL), is a novel HIV-1 integrase inhibitor, which is now approved for use in combination regimens for the treatment of HIV infection[1]
  - It has demonstrated potent efficacy (Figures 1-4) and a favorable safety profile in treatment-naïve and heavily treatment-experienced HIV-1 infected patients[2,3]
- This presentation is to evaluate the efficacy and safety of RAL in patients co-infected with HIV-1 and Hepatitis B and/or C enrolled in 3 phase III studies:
  - STARTMRK: HIV treatment-naïve patients
  - BENCHMRK-1 & 2 combined: HIV-treatment-experienced patients

Overall Efficacy through Week 96
Proportion (%) of Patients (95% CI) with HIV RNA <50 copies/mL (Non-Completer = Failure†)

Figure 1. STARTMRK[2]

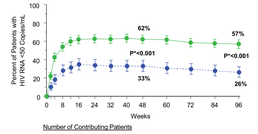


Number of Contributing Patients

Raltegravir + TFV/FTC	281	281	281	279	278	280	280	281	281	280	281
Efavirenz + TFV/FTC	282	282	281	282	280	281	281	282	282	281	282

† Non-completer = failure (NC=F); all discontinuations were counted as failures.

Figure 2. BENCHMRK[3]-1 & 2



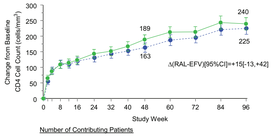
Number of Contributing Patients

Raltegravir + OBT	462		461		459							460
Placebo + OBT	237		237		237							237

* p-value was derived from a logistic regression model adjusted for baseline HIV RNA level ($\log_{10}$), first enfuvirtide use in OBT, first darunavir use in OBT, active PI in OBT.
† Non-completer = failure (NC=F); all discontinuations were counted as failures.

Change from Baseline in CD4 Cell Count
(Observed Failure†)

Figure 3. STARTMRK[2]

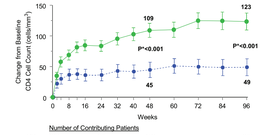


Number of Contributing Patients

Raltegravir + TFV/FTC	281	277	270	266	260	259	258	260	255	252	249
Efavirenz + TFV/FTC	281	272	269	266	260	254	251	248	252	248	243

† Observed Failure (OF): only discontinuations due to lack of efficacy were counted as failures afterwards, and baseline value was carried forward.

Figure 4. BENCHMRK[3] -1 & 2



Number of Contributing Patients

Raltegravir + OBT	462		435		439							420
Placebo + OBT	237		230		228							219

* p-value was derived from a mixed-effects model adjusted for: baseline CD4 cell count, stratum, treatment, visit, interactions between visit and previous variables.
† Observed Failure (OF): only discontinuations due to lack of efficacy were counted as failures afterwards, and baseline value was carried forward.

Methods

- Studies Included
  - STARTMRK: Phase III study in ART-naïve subjects, raltegravir (RAL) 400 mg bid vs efavirenz 600 mg qd (1:1 randomization), both with tenofovir + emtricitabine
  - BENCHMRK-1 & 2 combined: Identical phase III studies in highly treatment experienced patients failing current therapy, RAL 400 mg bid vs placebo (2:1 randomization), both with optimized background therapy
- Included patients with chronic HBV and/or HCV co-infection,
  - defined as:
    - HBV: + HBs antigen
    - HCV: + HCV antibody
      - In STARTMRK, most patients had +HCV RNA
  - patients were stable and met LFT entry criteria:
    - AST/ALT/Alkaline phosphatase ≤ 5x ULN
    - Total bilirubin ≤ 2x ULN (BENCHMRK-1 & 2)

Statistical Analysis

- Efficacy Analysis:
  - Observed failure (OF) approach used for subgroup efficacy analysis in order to focus on virologic responses (only patients who discontinued therapy due to lack of efficacy were considered failures), although primary analyses used non-completer = failure (NC=F) approach.
- Safety Analysis:
  - Given the imbalance in exposure in the BENCHMRK studies, exposure-adjusted event rates (number of patients with event /100 patient-years exposure) were summarized for adverse events.

Results

Baseline Patient Characteristics

STARTMRK

	Hepatitis B/C Positive		Hepatitis B/C Negative	
	RAL (N=18)	EFV (N=16)	RAL (N=263)	EFV (N=266)
Median age, years	37.0	35.5	37.0	36.0
Male, n (%)	16 (88.9)	11 (68.8)	211 (80.2)	220 (82.7)
Race: White, n (%)	6 (33.3)	5 (31.3)	110 (41.8)	118 (44.4)
Black, n (%)	3 (16.7)	1 (6.3)	30 (11.4)	22 (8.3)
Asian, n (%)	3 (16.7)	6 (37.5)	33 (12.5)	26 (9.8)
Hispanic, n (%)	4 (22.2)	3 (18.8)	56 (21.3)	64 (24.1)
Other, n (%)	2 (11.1)	1 (6.3)	34 (12.9)	36 (13.5)
AIDS, n (%)	1 (5.6)	7 (43.8)	42 (16.0)	36 (13.5)
Median CD4 cell count, cells/μL	196.5	101.5	213.0	208.0
Median HIV RNA, copies/mL	98350	90950	117000	104500
Hepatitis B only, n (%)	13 (72.2)	9 (56.3)	---	---
Hepatitis C only, n (%)	5 (27.7)	6 (37.5)	---	---
Hepatitis B and C, n (%)	0	1 (6.3)	---	---

---, not applicable.

BENCHMRK-1 & 2

	Hepatitis B/C Positive		Hepatitis B/C Negative	
	RAL (N=77)	Placebo (N=37)	RAL (N=385)	Placebo (N=200)
Median age, years	44.0	42.0	45.0	45.0
Male, n (%)	67 (87.0)	34 (91.9)	338 (87.8)	176 (88.0)
Race: White, n (%)	57 (74.0)	30 (81.1)	244 (63.4)	143 (71.5)
Black, n (%)	9 (11.7)	4 (10.8)	56 (14.5)	22 (11.0)
Asian, n (%)	4 (5.2)	1 (2.7)	12 (3.1)	5 (2.5)
Hispanic, n (%)	5 (6.5)	1 (2.7)	48 (12.5)	18 (9.0)
Other, n (%)	2 (2.6)	1 (2.7)	25 (6.5)	12 (6.0)
AIDS, n (%)	70 (90.9)	31 (83.8)	357 (92.7)	184 (92.0)
Median CD4 cell count, cells/μL	165.0	125.0	111.5	123.0
Median HIV RNA, copies/mL	44200	48000	67000	44450
Median # of prior ARTs	12	12	12	12
Median yrs prior ART use	10.5	10.5	9.9	10.2
Hepatitis B only, n (%)	36 (46.8)	7 (18.9)	---	---
Hepatitis C only, n (%)	37 (48.1)	28 (75.7)	---	---
Hepatitis B and C, n (%)	4 (5.2)	2 (5.4)	---	---

---, not applicable.
† Among patients with Hepatitis B, 92% took tenofovir. Of these, 75% also took emtricitabine, 20% took lamivudine, and 5% took neither emtricitabine nor lamivudine.

Efficacy at Week 96 by Hepatitis Co-infection Status

HIV RNA <50 copies/mL[§]

		STARTMRK		BENCHMRK-1 & 2	
Hepatitis Co-infection		RAL #	EFV #	RAL *	PBO *
Yes	% (n/N) [95% CI]	93 (14/15) [68, 100]	92 (12/13) [64, 100]	63 (41/65) [50, 75]	15 (5/34) [5, 31]
No	% (n/N) [95% CI]	90 (214/238) [85, 93]	89 (210/235) [85, 93]	61 (221/360) [56, 66]	31 (57/186) [24, 38]

§ Observed Failure (OF) approach: only discontinuations due to lack of efficacy were counted as failures afterwards, and baseline value was carried forward.
# with tenofovir + FTC; * with optimized background therapy

Change from Baseline in CD4 Count (cells/uL)[§]

		STARTMRK		BENCHMRK-1 & 2	
Hepatitis Co-infection		RAL #	EFV #	RAL *	PBO *
Yes	cells/μL (95% CI)	218 [114, 323]	257 [188, 325]	106 [72, 140]	30 [4, 57]
No	cells/μL (95% CI)	241 [221, 261]	223 [203, 243]	127 [111, 142]	52 [37, 68]

§ Observed Failure (OF) approach: only discontinuations due to lack of efficacy were counted as failures afterwards, and baseline value was carried forward.
# with tenofovir + FTC; * with optimized background therapy

Safety by Hepatitis Co-infection Status

Clinical Adverse Event Summary

	STARTMRK				BENCHMRK-1 & 2			
	Hepatitis B/C +		Hepatitis B/C -		Hepatitis B/C +		Hepatitis B/C -	
	RAL (N=18)	EFV (N=16)	RAL (N=263)	EFV (N=266)	RAL (N=77)	Pbo (N=37)	RAL (N=385)	Pbo (N=200)
PYR at risk	---	---	---	---	125	33	584	210
	%	%	%	%	% (rate†)	% (rate†)	% (rate†)	% (rate†)
Clinical AE	94.4	93.8	94.3	97.4	92.2 (56.8)	83.8 (93.9)	92.5 (61.0)	89.5 (85.2)
Drug-related*	50.0	75.0	46.8	78.2	54.5 (33.6)	59.5 (66.7)	58.4 (38.5)	58.5 (55.7)
Serious	16.7	0	12.9	12.4	23.4 (14.4)	18.9 (21.2)	23.1 (15.2)	23.0 (21.9)
Serious & drug-related*	0	0	2.3	1.9	5.2 (3.2)	2.7 (3.0)	2.3 (1.5)	4.0 (3.8)
Discontinued	5.6	0	3.4	6.4	3.9 (2.4)	2.7 (3.0)	3.6 (2.4)	5.0 (4.8)

† per 100 person-years at risk (PYR).
* determined by investigator to be possibly, probably, or definitely related to raltegravir, placebo, or efavirenz alone or in combination with other ART.

Selected Laboratory Abnormalities

		STARTMRK				BENCHMRK-1 & 2			
		Hepatitis B/C +		Hepatitis B/C -		Hepatitis B/C +		Hepatitis B/C -	
		RAL (N=18)	EFV (N=16)	RAL (N=263)	EFV (N=266)	RAL (N=77)	Pbo (N=37)	RAL (N=385)	Pbo (N=200)
		%	%	%	%	% (rate†)	% (rate†)	% (rate†)	% (rate†)
AST	Grade								
2.6 - 5.0 x ULN	2	5.6	18.8	3.8	4.6	18.2 (11.2)	10.8 (12.1)	7.0 (4.6)	6.5 (6.2)
5.1 - 10.0 x ULN	3	5.6	0.0	1.5	2.3	7.8 (4.8)	2.7 (3.0)	3.4 (2.2)	3.0 (2.9)
>10.0 x ULN	4	5.6	6.3	0.8	0.0	2.6 (1.6)	0.0 (0.0)	0.3 (0.2)	1.5 (1.4)
ALT									
2.6 - 5.0 x ULN	2	22.2	12.5	4.9	8.4	20.8 (12.8)	10.8 (12.1)	6.5 (4.3)	9.0 (8.6)
5.1 - 10.0 x ULN	3	0.0	6.3	0.8	1.5	9.1 (5.6)	8.1 (9.1)	2.9 (1.9)	1.0 (1.0)
>10.0 x ULN	4	5.6	6.3	0.8	0.4	3.9 (2.4)	0.0 (0.0)	0.8 (0.5)	2.0 (1.9)
Total bilirubin									
1.6 - 2.5 x ULN	2	16.7	0.0	2.7	0.0	9.1 (5.6)	2.7 (3.0)	4.9 (3.3)	3.0 (2.9)
2.6 - 5.0 x ULN	3	0.0	0.0	0.8	0.0	2.6 (1.6)	5.4 (6.1)	2.9 (1.9)	2.0 (1.9)
>5.0 x ULN	4	0.0	0.0	0.0	0.0	1.3 (0.8)	0.0 (0.0)	0.8 (0.5)	0.0 (0.0)

† per 100 person-years at risk (PYR).

Hepatobiliary Adverse Events

	STARTMRK				BENCHMRK-1 & 2			
	Hepatitis B/C +		Hepatitis B/C -		Hepatitis B/C +		Hepatitis B/C -	
	RAL (N=18)	EFV (N=16)	RAL (N=263)	EFV (N=266)	RAL (N=77)	Pbo (N=37)	RAL (N=385)	Pbo (N=200)
	%	%	%	%	% (rate†)	% (rate†)	% (rate†)	% (rate†)
Any hepatobiliary AE	0	0	3.0	0.4	2.6 (1.6)	5.4 (6.1)	3.9 (2.6)	4.0 (3.8)
Hepatic failure, acute	--	--	--	--	--	--	0.3 (0.2)	0
Hepatic pain	--	--	--	--	--	--	0.3 (0.2)	0
Hepatic steatosis	--	--	0.4	0	--	--	0.3 (0.2)	0
Hepatitis	--	--	0	0.4	1.3 (0.8)	0	0.3 (0.2)	1.0 (1.0)
Hepatomegaly	--	--	1.1	0	--	--	0.5 (0.3)	1.5 (1.4)
Hyperbilirubinemia	--	--	--	--	--	--	0.5 (0.3)	0
Jaundice	--	--	0.4	0	--	--	0.3 (0.2)	0.5 (0.5)
Portal hypertension	--	--	--	--	--	--	0.5 (0.3)	0
Bile duct stone	--	--	--	--	1.3 (0.8)	0	--	--
Cholangitis	--	--	--	--	--	--	0.3 (0.2)	0
Cholecystitis	--	--	0.8	0	--	--	0.3 (0.2)	0.5 (0.5)
Cholelithiasis	--	--	0.4	0	0	5.4 (6.1)	0.5 (0.3)	0.5 (0.5)
Cholestasis	--	--	--	--	--	--	0	0.5 (0.5)
Gallbladder disorder	--	--	--	--	--	--	0	0.5 (0.5)
Gallbladder polyp	--	--	--	--	--	--	0.3 (0.2)	0

† per 100 person-years at risk (PYR).
* indicates no event in either treatment group.

Conclusions

- RAL was efficacious in HIV-infected patients with and without Hepatitis B and/or Hepatitis C co-infection.
- RAL was generally well tolerated in HIV-infected patients with and without Hepatitis B and/or Hepatitis C co-infection.
  - Grade 2, 3, 4 liver enzyme elevations were observed more frequently in HIV/HBV/HCV co-infected patients than in HIV-monoinfected patients, but this difference was noted in both the RAL and control groups (EFV in STARTMRK and OBT in BENCHMRK-1 & 2).

Copyright © 2010 Merck & Co., Inc., Whitehouse Station, New Jersey, USA, All Rights Reserved