Bonaventura Clotet
Hospital Universitari Germans Trias i Pujol and irsiCaixa Foundation
UAB
Barcelona
Spain
BClotet@irsicaixa.es

Safety and tolerability of etravirine in hepatitis B and/or C co-infected patients in DUET-1 and DUET-2: pooled 48-week results

P272

Bonaventura Clotet,[1] Christine Katlama,[2] Adriano Lazzarin,[3] Katrien Janssen,[4] Thomas N Kakuda,[5] Goedele De Smedt[4]

[1]Hospital Universitari Germans Trias i Pujol and irsiCaixa Foundation, UAB, Barcelona, Spain; [2]Groupe Hospitalier Pitié-Salpétrière, Paris, France; [3]Vita-Salute, San Raffaele University, Milan, Italy; [4]Tibotec BVBA, Mechelen, Belgium; [5]Tibotec Inc., Yardley, PA, USA

Abstract

The 48-week efficacy and safety analysis of the next-generation NNRTI etravirine (ETR; TMC125) in the DUET studies has recently been completed. We report safety results from a planned pooled analysis, according to baseline hepatitis co-infection status.

HIV-1-infected patients on stable, but virologically failing therapy were randomised to receive either ETR 200mg bid or placebo, both in combination with a background regimen (BR) consisting of darunavir with low-dose ritonavir (DRV/r), investigator-selected NRTIs and optional enfuvirtide (ENF). Hepatitis B and/or C virus (HBV and/or HCV) co-infection status was confirmed by hepatitis B surface antigen or HCV antibody and qualitative HCV RNA. Co-infected patients were eligible if they were clinically stable, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <5 x the upper limit of normal and did not require antihepatitis treatment. Adverse events (AEs) and laboratory parameters were analysed.

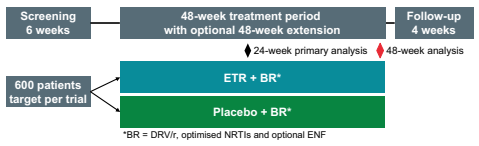
At baseline, HBV and/or HCV status was known for 1,130 HIV-1-infected patients. Of these, 140 patients (12.3%) were co-infected with HBV and/or HCV; the sample size was too small to compare HBV and HCV groups separately. Median treatment duration for this analysis was 52.3 vs 51.0 weeks in the ETR + BR and placebo + BR groups, respectively. In co-infected patients, grade 3 or 4 AEs, serious AEs and deaths were less frequent with ETR than with placebo. Grade 3 or 4 AST/ALT elevations were more frequent in co-infected patients receiving ETR, however the differences between the ETR and placebo groups was small. The incidence of grade 3 or 4 hepatic AEs was similar in both treatment groups.

	HIV and HBV and/or HCV co-infected patients		Not co-infected patients	
	ETR + BR (n=72)	Placebo + BR (n=68)	ETR + BR (n=494)	Placebo + BR (n=496)
Any AEs	95.8	97.0	95.7	95.8
Grade 3 or 4 AEs	31.9	44.1	32.8	33.5
Discontinuation due to AEs	8.3	8.8	6.7	5.0
Serious AEs	26.4	33.8	18.2	21.8
Deaths	2.8	4.4	1.4	2.8
Hepatic AEs*	12.5	8.8	5.5	6.0
Grade 3 or 4 hepatic AEs	6.9	7.3	2.4	2.4
Discontinuation due to hepatic AE	1.4	2.9	0.8	0.4
Selected treatment-emergent grade 3 or 4 laboratory parameters				
ALT	11.1	7.3	2.4	1.4
AST	9.7	5.8	2.2	1.4

HBV and/or HCV status was not recorded in 40 placebo- and 33 ETR-treated patients.
*Data also includes hepatic laboratory abnormalities reported as AEs

In general, the incidence and severity of AEs with ETR was similar to placebo, irrespective of co-infection status. The incidence of hepatic AEs and grade 3 or 4 AST/ALT elevations was higher in co-infected patients than in not co-infected patients in both treatment groups, consistent with the underlying chronic hepatitis condition. ETR did not increase hepatic toxicity in patients with hepatitis co-infection and was generally well tolerated in all patients.

DUET study design and major inclusion criteria



- Plasma viral load >5,000 copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historical genotype
- ≥3 primary PI mutations at screening
- Hepatitis B and/or C co-infected patients were eligible for inclusion if they were clinically stable, with AST and ALT levels <5 x the upper limit of normal, and did not require any antihepatitis treatment. Patients with acute viral hepatitis were excluded
- DUET-1 and DUET-2 differ only in geographical location
- Pooled analysis was prespecified

RAM = resistance-associated mutation; PI = protease inhibitor

Baseline demographics

Parameter, %	ETR + BR: Co-infected (n=72)	ETR + BR: Not co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Not co-infected (n=496)
Gender				
Male	93	89	87	89
Race*	(n=61)	(n=442)	(n=59)	(n=443)
Caucasian	69	70	80	69
Black	18	13	8	13
Hispanic	7	12	8	13

*Local regulations in some countries prohibited the collection of ethnic information

- Hepatitis co-infection status
  - positive hepatitis B surface antigen: 7% ETR + BR vs 6% placebo + BR
  - known active HCV infection:‡ 6% in both ETR and placebo groups
  - hepatitis B and/or C co-infection status:§ 13% ETR + BR vs 12% placebo + BR

‡Determined based on positive HCV antibody and qualitative HCV RNA results; §Defined as having a positive hepatitis B antibody test and/or a known active HCV infection; Sample size was too small to compare HBV and HCV groups separately

Baseline disease characteristics

Parameter	ETR + BR: Co-infected (n=72)	ETR + BR: Not co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Not co-infected (n=496)
Median duration of HIV infection, years (range)	15 (2.6–23.4)	14* (2.7–25.5)	15 (7.9–25.3)	14‡ (4.7–26.3)
CDC category C, %	67	56	59	59
Median viral load, $\log_{10}$ copies/mL (range)	4.8 (3.3–6.2)	4.8 (2.7–6.8)	4.9 (2.2–5.9)	4.8 (2.4–6.3)
Median CD4 cell count, cells/mm³ (range)	92.5 (1–666)	119.5 (1–789)	101.5 (1–801)	121.5 (0–912)
CD4 cell count <50 cells/mm³, %	32	36	37	33
Viral load ≥100,000 copies/mL, %	35	38	38	34

*n=492; ‡n=495

CDC = Centers for Disease Control and Prevention

Overview of AEs (regardless of causality) by hepatitis B and/or C co-infection status

Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Not co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Not co-infected (n=496)
Any AE (any cause)	69 (96)	473 (96)	66 (97)	475 (96)
Grade 3 or 4 AE	23 (32)	162 (33)	30 (44)	166 (33)
Treatment-related AE	43 (60)	257 (52)	27 (40)	240 (48)
Serious AE (SAE)	19 (26)	90 (18)	23 (34)	108 (22)
Discontinuation due to AE	6 (8)	33 (7)	6 (9)	25 (5)
Death (any cause)*	2 (3)	7 (1)	3 (4)	14 (3)
AEs of interest				
Hepatic AEs	9 (13)	27 (5)	6 (9)	30 (6)
Rash (any type)	15 (21)	95 (19)	7 (10)	54 (11)
Neuropsychiatric AEs	19 (26)	154 (32)	21 (31)	172 (35)

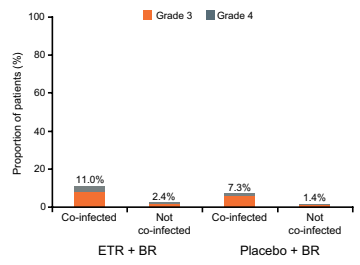
*All deaths in the ETR + BR group were considered not or doubtfully related to ETR. One death in the pooled placebo + BR group was considered possibly related to the BR

Incidence of hepatic AEs by hepatitis B and/or C co-infection status

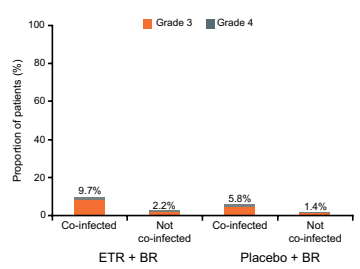
Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Not co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Not co-infected (n=496)
Any hepatic AE	9 (13)	27 (5)	6 (9)	30 (6)
Any treatment-related hepatic AE	4 (6)	15 (3)	3 (4)	14 (3)
Any hepatic SAE	1 (1)	5 (1)	2 (3)	6 (1)
Permanent discontinuation due to hepatic AEs	1 (1)	4 (1)	2 (3)	2 (<1)
Any grade 3 or 4 hepatic AE	5 (7)	12 (2)	5 (7)	12 (2)
Grade 3 or 4 ↑ALT	8 (11)	12 (2)	5 (7)	7 (1)
Grade 3 or 4 ↑AST	7 (10)	11 (2)	4 (6)	7 (1)
Grade 3 or 4 hyperbilirubinaemia	4 (6)	6 (1)	1 (1)	2 (<1)

Co-infection status was not recorded in 33 ETR-treated and 40 placebo-treated patients

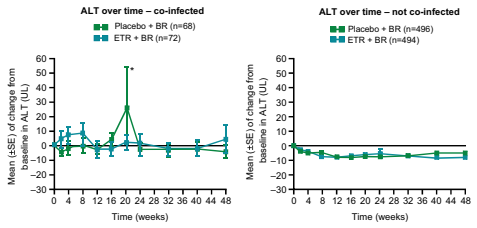
Grade 3 and 4 elevations in ALT by hepatitis B and/or C co-infection status



Grade 3 and 4 elevations in AST by hepatitis B and/or C co-infection status

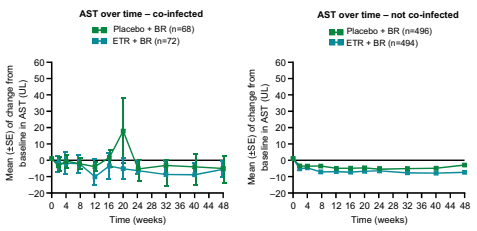


ALT changes over 48 weeks by hepatitis B and/or C co-infection status



*The spike is due to one patient in the placebo + BR group with an extreme ALT value (1,581UL) at Week 20; SE = standard error

AST changes over 48 weeks by hepatitis B and/or C co-infection status



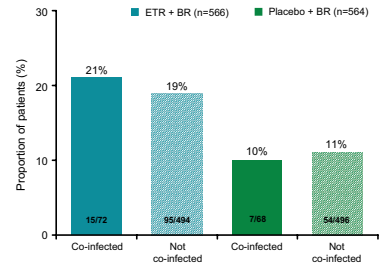
*The spike is due to one patient in the placebo + BR group with an extreme AST value (1,185UL) at Week 20

Hepatobiliary AEs by hepatitis B and/or C co-infection status

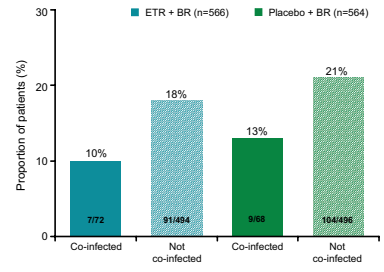
Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Not co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Not co-infected (n=496)
Any hepatobilliary disorder	5 (7)	11 (2)	1 (1)	17 (3)
Acute hepatic failure	0	1 (<1)	0	0
Cholangitis	0	0	0	2 (<1)
Cholecystitis	0	1 (<1)	0	2 (<1)
Cholecystitis acute	0	1 (<1)	0	0
Cholecystitis chronic	0	0	0	1 (<1)
Cholelithiasis	0	0	0	2 (<1)
Cytolytic hepatitis	1 (1)	1 (<1)	0	0
Hepatic cirrhosis	1 (1)	0	0	1 (<1)
Hepatic cyst	1 (1)	0	0	0
Hepatic steatosis	0	2 (<1)	0	1 (<1)
Hepatitis	1 (1)	0	1 (1)	1 (<1)
Hepatomegaly	0	5 (1)	0	5 (1)
Hepatosplenomegaly	1 (1)	0	0	2 (<1)
Hyperbilirubinaemia	0	1 (<1)	0	1 (<1)
Jaundice	1 (1)	3 (<1)	0	2 (<1)

Analysis does not include laboratory abnormalities reported as AEs

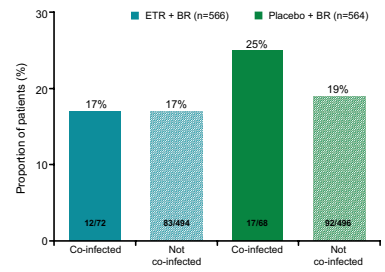
Incidence of rash (any type) by hepatitis B and/or C co-infection status



Incidence of nervous system AEs by hepatitis B and/or C co-infection status



Incidence of psychiatric system AEs by hepatitis B and/or C co-infection status



Conclusions

- In general, the incidence and severity of AEs with ETR + BR was similar to placebo + BR, irrespective of hepatitis co-infection status
  - 96% of not co-infected patients reported any AE in both treatment groups
  - 96% of co-infected patients reported any AE in the ETR group vs 97% in the placebo group
- In co-infected patients, grade 3 or 4 AEs and SAEs were less frequent with ETR + BR than with placebo + BR and discontinuations were low
- While hepatic AEs and elevated ALT/AST were most frequent in co-infected patients in the ETR group, the difference between ETR and placebo groups was small
- The incidence of rash, although higher in ETR- than placebo-treated patients, occurred with a similar incidence in co-infected and not co-infected patients in each treatment group
- The incidence of nervous and psychiatric system AEs was lower in patients receiving ETR + BR than those receiving placebo + BR, irrespective of co-infection status

Acknowledgements

- We express our gratitude to the patients who participated in the studies, as well as the study centre staff, the data safety and monitoring board, clinical event adjudication panels, Virco, Tibotec personnel and the following principal investigators

DUET-1

Argentina: HA Ariza, J Benetucci, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso, P Patterson, RA Teijeiro; **Brazil:** CA da Cunha, B Grinsztejn, EG Kallas, JV Madruga, EM Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** AA Avilés Montoya, G Herrera Martínez, A Solano Chinchilla; **France:** M Dupon, C Katlama, JM Livrozet, P Morlat, G Pialoux, C Piketty, I Poizot-Martin; **Mexico:** J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero; **Panama:** A Canton, A Rodriguez, N Sosa; **Puerto Rico:** IO Morales Ramirez, JL Santana Bagur, R Soto-Malave; **Thailand:** T Anekthananon, P Mootsikapun, K Ruxrungtham; **USA:** M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, WJ Fessel, R Haubrich, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Lalezari, J Leider, D McDonough, A Mills, K Mounzer, J Nadler, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wilkin, T Wills, M Wohlfeiler, K Workowski

DUET-2

Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, B Trottier, CM Tsoukas, S Walmsley; **France:** C Arvieux, L Cotte, JF Delfraissy, C Katlama, PM Girard, B Marchou, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arasteh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, B Clotet, G Garcia, JM Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, M Johnson, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, T Campbell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, RN Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch

Supported by Tibotec

Presented at the 9th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 9–13 November 2008.

This poster is available on-line at www.tibotec.com