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Etravirine demonstrates a favourable safety and tolerability profile versus placebo irrespective of hepatitis co-infection: Week 96 analysis from the DUET trials

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Abstract

Objectives

Etravirine (ETR; TMC125) has demonstrated long-term, durable efficacy, with a safety profile similar to placebo in treatment-experienced, HIV-1-infected patients. We report 96-week pooled safety and tolerability data from the Phase III DUET trials in patients co-infected with hepatitis B and/or C virus (HBV/HCV).

Methods

Stable, virologically failing HIV-1-infected patients with documented resistance were randomised to either ETR 200mg bid or placebo, with a background regimen (BR) of darunavir with low-dose ritonavir (DRV/r), investigator-selected NRTIs ± enfuvirtide (ENF). HBV/HCV co-infection status was confirmed by hepatitis B surface antigen or HCV antibody and qualitative HCV ribonucleic acid. Co-infected patients were eligible if they did not require anti-hepatitis treatment and were clinically stable, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <5 x the upper limit of normal (ULN). Adverse events (AEs) and laboratory parameters were analysed.

Results

Co-infection data were available for 566 ETR + BR and 564 placebo + BR patients, of which 12.4% were co-infected with HBV/HCV. Sample numbers were too small to allow individual HBV and HCV analyses. In co-infected patients, the incidence of grade 3 or 4 AEs, serious AEs (SAEs) and deaths was comparable among the treatment groups. Consistent with the underlying hepatitis co-infection, the incidence of hepatic AEs and grade 3 or 4 AST/ALT elevations was higher in co-infected patients than in non-co-infected patients in both treatment groups; co-infected patients in the ETR + BR group reported the highest incidence of hepatic events although discontinuation due to hepatic AEs was low and comparable between the treatment groups.

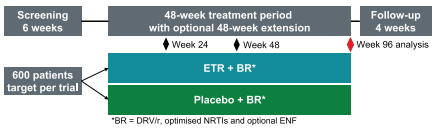
Parameter	HBV and/or HCV co-infected patients: ETR + BR (n=72)	HBV and/or HCV co-infected patients: Placebo + BR (n=68)	Non-co-infected patients: ETR + BR (n=494)	Non-co-infected patients: Placebo + BR (n=496)
Median treatment duration, weeks	96.0	90.0	96.0	70.0
Total patient-years of exposure	104.3	92.7	744.4	627.4
Any AE, %	96	97	97	96
Grade 3 or 4 AEs	43	46	40	35
Discontinuation due to AEs	10	9	8	5
SAEs	35	37	25	24
Deaths	4	4	3	3
Hepatic AEs, %	18	15	7	6
Grade 3 or 4 hepatic AEs	11	7	3	2
Serious hepatic AEs	4	4	1	1
Discontinuation due to hepatic AE	3	3	1	<1
Selected treatment-emergent grade 3 or 4 laboratory parameters, %				
ALT	14	9	3	2
AST	11	7	3	2

HBV and/or HCV status was not recorded in 40 placebo- and 33 ETR-treated patients; these patients are not included in the analysis

Conclusions

Patients co-infected with HBV/HCV reported a higher incidence of hepatic AEs and grade 3 or 4 ALT/AST elevations versus those patients not co-infected. The incidence and severity of overall AEs with ETR + BR was comparable to placebo + BR, regardless of co-infection status.

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
- HBV and/or HCV co-infected patients were eligible for inclusion if they were clinically stable, with AST and ALT levels <5 x the ULN, and did not require any anti-hepatitis treatment. Patients with acute viral hepatitis were excluded
- DUET-1 and DUET-2 differ only in geographical location
- Pooled analysis was prespecified
- 2% of randomised patients completed the trial at Week 48 and elected not to continue into the open-label extension phase

RAM = resistance-associated mutation; PI = protease inhibitor

Baseline demographics

Parameter	ETR + BR: Co-infected (n=72)	ETR + BR: Non-co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Non-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

- HBV and/or HCV co-infection status:[†] 13% ETR + BR vs 12% placebo + BR
  - positive hepatitis B surface antigen: 7% ETR + BR vs 6% placebo + BR
  - known chronic HCV infection:[‡] 6% in both ETR and placebo groups

[†]Defined as having a positive hepatitis B surface antigen test and/or a known chronic HCV infection (co-infection status was not recorded in 33 ETR-treated and 40 placebo-treated patients)
[‡]Determined based on positive HCV antibody and qualitative HCV RNA results

Baseline disease characteristics

Parameter	ETR + BR: Co-infected (n=72)	ETR + BR: Non-co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Non-co-infected (n=496)
Median duration of HIV infection, years (range)	15 (2.5–23.4)	14* (2.6–25.4)	15 (7.8–25.1)	14‡ (4.7–26.2)
CDC category C, %	67	56	59	59
Median viral load, $\log_{10}$ copies/mL (range)	4.8 (3.4–6.2)	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 HBV and/or HCV co-infection status

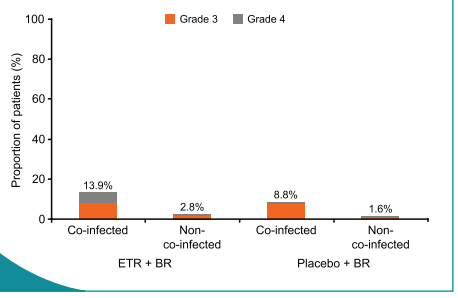
Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Non-co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Non-co-infected (n=496)
Median treatment duration, weeks	96.0	96.0	90.0	70.0
Total patient-years of exposure	104.3	744.4	92.7	627.4
Any AE	69 (96)	477 (97)	66 (97)	477 (96)
Grade 3 or 4 AE	31 (43)	200 (40)	31 (46)	176 (35)
Any treatment-related AE	45 (63)	275 (56)	27 (40)	242 (49)
SAE	25 (35)	123 (25)	25 (37)	119 (24)
Discontinuation due to AE	7 (10)	40 (8)	6 (9)	27 (5)
Death (any cause)*	3 (4)	13 (3)	3 (4)	15 (3)
AEs of interest				
Hepatic AEs	13 (18)	36 (7)	10 (15)	32 (6)
Rash (any type)	15 (21)	103 (21)	6 (9)	60 (12)
Neuropsychiatric AEs	22 (31)	169 (34)	23 (34)	182 (37)

*All deaths in the ETR + BR group were considered not or doubtfully related to ETR. One death in the placebo + BR group was considered possibly related to the BR. 'Treatment-related' refers to any AE related to any of the trial medication

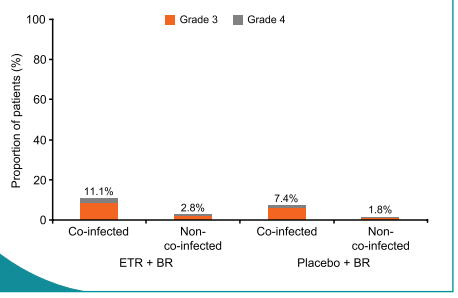
Incidence of hepatic AEs by HBV and/or HCV co-infection status

Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Non-co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Non-co-infected (n=496)
Any hepatic AE	13 (18)	36 (7)	10 (15)	32 (6)
Any treatment-related hepatic AE	4 (6)	15 (3)	3 (4)	15 (3)
Any hepatic SAE	3 (4)	7 (1)	3 (4)	6 (1)
Permanent discontinuation due to hepatic AEs	2 (3)	5 (1)	2 (3)	2 (<1)
Any grade 3 or 4 hepatic AE	8 (11)	16 (3)	5 (7)	12 (2)
Grade 3 or 4 elevated ALT	10 (14)	14 (3)	6 (9)	8 (2)
Grade 3 or 4 elevated AST	8 (11)	14 (3)	5 (7)	9 (2)
Grade 3 or 4 hyperbilirubinaemia	6 (8)	6 (1)	1 (1)	2 (<1)

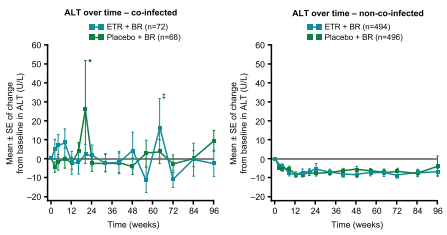
Grade 3 and 4 elevations in ALT by HBV and/or HCV co-infection status



Grade 3 and 4 elevations in AST by HBV and/or HCV co-infection status

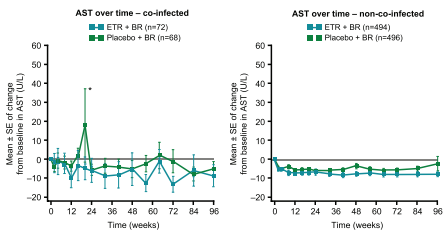


ALT changes over 96 weeks by HBV and/or HCV co-infection status



SE = standard error
*The spike is due to one patient in the placebo + BR group with an ALT value 1,581U/L at Week 20
‡The spike is due to one patient in the ETR + BR group with an ALT value 680U/L at Week 64

AST changes over 96 weeks by HBV and/or HCV co-infection status



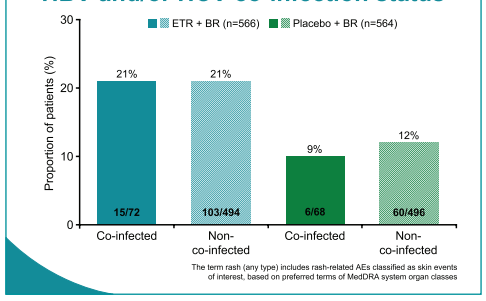
*The spike is due to one patient in the placebo + BR group with an AST value 1,185U/L at Week 20

Hepatobiliary AEs by HBV and/or HCV co-infection status

Parameter, n (%)	ETR + BR: Co-infected (n=72)	ETR + BR: Non-co-infected (n=494)	Placebo + BR: Co-infected (n=68)	Placebo + BR: Non-co-infected (n=496)
Any hepatobilliary disorder	7 (10)	16 (3)	4 (6)	18 (4)
Acute cholecystitis	0	1 (<1)	0	0
Acute hepatic failure	0	1 (<1)	0	0
Cholangitis	0	0	0	2 (<1)
Cholecystitis	0	3 (1)	1 (1)	2 (<1)
Cholelithiasis	0	1 (<1)	0	2 (<1)
Chronic cholecystitis	0	0	0	1 (<1)
Cytolytic hepatitis	1 (1)	1 (<1)	1 (1)	1 (<1)
Hepatic cirrhosis	1 (1)	0	1 (1)	1 (<1)
Hepatic cyst	1 (1)	0	0	0
Hepatic failure	1 (1)	1 (<1)	0	0
Hepatic steatosis	0	2 (<1)	0	1 (<1)
Hepatitis	1 (1)	0	1 (1)	1 (<1)
Hepatomegaly	1 (1)	5 (1)	0	5 (1)
Hepatosplenomegaly	1 (1)	1 (<1)	0	2 (<1)
Hyperbilirubinaemia	0	1 (<1)	0	1 (<1)
Jaundice	1 (1)	3 (<1)	0	2 (<1)

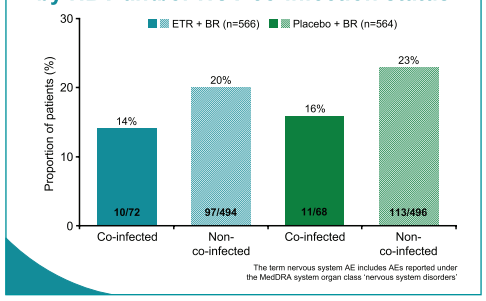
Analysis does not include laboratory abnormalities reported as AEs

Incidence of rash (any type) by HBV and/or HCV co-infection status



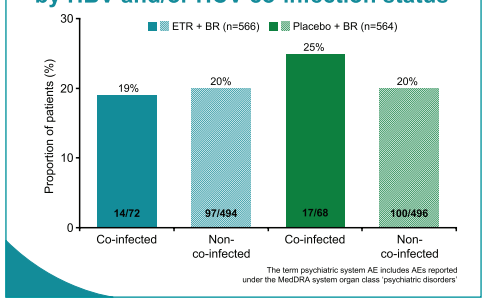
The term rash (any type) includes rash-related AEs classified as skin events of interest, based on preferred terms of MedDRA system organ classes

Incidence of nervous system AEs by HBV and/or HCV co-infection status



The term nervous system AE includes AEs reported under the MedDRA system organ class 'nervous system disorders'

Incidence of psychiatric system AEs by HBV and/or HCV co-infection status



The term psychiatric system AE includes AEs reported under the MedDRA system organ class 'psychiatric disorders'

Conclusions

- In general, the incidence and severity of AEs with ETR + BR was similar to placebo + BR, irrespective of hepatitis co-infection status
- Consistent with the underlying hepatitis co-infection status, there was a higher incidence of hepatic AEs and elevated ALT/AST in co-infected patients than non-co-infected patients
  - however, ETR + BR did not appear to increase hepatic risk in co-infected patients
- The incidence of rash, although higher in ETR- than placebo-treated patients, occurred with a similar incidence in co-infected and non-co-infected patients in each treatment group
- The incidence of nervous and psychiatric system AEs was similar between the ETR and placebo groups, irrespective of co-infection status
- These results confirm the observations at 48 weeks, providing evidence over the longer term that ETR is generally safe and well tolerated regardless of hepatitis co-infection status

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