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Impact of etravirine on hospitalizations and hospital-related costs: 48-week findings from pooled DUET trials

Kelly Gebo,[1] Silas Martin,[2] Chris Corbett,[3] Goedele De Smedt[3]

[1]Johns Hopkins University, Baltimore, MD, USA; [2]Johnson & Johnson Pharmaceutical Services LLC, Mechelen, Belgium; [3]Tibotec BVBA, Mechelen, Belgium

Presenting author:
Silas Martin, MS
Johnson & Johnson
Pharmaceutical Services LLC
Mechelen
Belgium
smartinc@janbe.jnj.com

Abstract

Background
DUET-1 and DUET-2 are two identically designed, ongoing, randomized, double-blind, placebo-controlled, Phase III trials, which have demonstrated superiority of etravirine (ETR; TMC125) + background regimen (BR; darunavir/low-dose ritonavir [DRV/r], NRTI[s] and optional enfuvirtide [ENF]) versus placebo + BR in HIV-1-infected, treatment-experienced patients. Efficacy and safety results from DUET-1 and DUET-2 have been reported recently. Hospitalization events and duration of hospital stay were recorded for each patient.

Methods
This analysis evaluated, at 48 weeks, differences in hospitalizations and days hospitalized to examine the cost implications between ETR + BR and placebo + BR in the pooled DUET trial population. Hospitalization rates were analyzed by negative binomial regression, examining the effect of baseline CD4 cell count strata. Daily hospital costs were assigned over the range of published estimates of US$1308–2441 (excluding antiretroviral treatment), which had been inflated to 2006 costs.

Results
One thousand, two hundred and three patients were included: 599 vs 604 in the ETR versus placebo groups. Baseline characteristics and average follow-up were comparable between arms. The number (%) of patients hospitalized was 105 (17.5%) vs 139 (23.0%) for ETR + BR versus placebo + BR, respectively (p=0.0006). Hospitalization rates and number of hospitalization days increased with decreasing baseline CD4 cell counts in both arms. For patients with <50 cells/mm^3 CD4 cell count at baseline, ETR + BR showed a statistically significant decrease in the hospitalization rate versus placebo + BR (p=0.0001). Total hospital days observed during the 48-week follow-up period were 1702 vs 2747 for ETR + BR versus placebo + BR. Hospital costs were estimated to be $2.2–4.2 million for ETR + BR vs $3.6–6.7 million for placebo + BR.

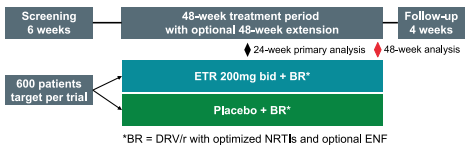
Conclusions
At Week 48, ETR + BR provided a statistically significant reduction in overall hospitalizations rates versus placebo + BR. The reductions in the number of hospitalizations and time spent in the hospital represent clinical benefit to the patients and significant savings in hospital-related costs to the healthcare system.

Please note the abstract has been updated since submission.

Introduction

- The cost of HIV-related healthcare in the US has historically been high, with the greatest cost driver in many cases being inpatient hospitalizations
- The advent of highly active antiretroviral therapy (HAART) has reduced morbidity and inpatient utilization
- Despite HAART, hospitalization remains an issue for people living with HIV, and it is important to continue to examine the impact that current antiretroviral (ARV) treatment has on hospitalizations among HIV-infected patients
- The Phase III DUET trials evaluated the efficacy and safety of ETR + BR versus placebo + BR in treatment-experienced HIV-1-infected patients
- This analysis assessed the effect of ETR + BR on hospitalization rate, length of hospitalization and hospitalization costs using pooled DUET 48-week data

DUET study design and major inclusion criteria



*BR = DRV/r with optimized NRTIs and optional ENF

- Plasma viral load >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historic genotype
- ≥3 primary PI mutations at screening
- DUET-1 and DUET-2 differ only in geographic location
  - in DUET-1, patients were recruited from Thailand, Europe and the Americas
  - in DUET-2, patients were recruited from Europe, Australia, Canada and the USA
- Pooled analysis was prespecified

RAM = resistance-associated mutation; PI = protease inhibitor

Hospitalization data

- Hospitalization events, reason for hospitalization and duration of hospital stay were recorded for each patient
  - hospital rates were standardized per 100 patient years of follow-up
- DUET study data provided information on patients' baseline characteristics, disease state and HIV risk group
- Duration of hospitalization was calculated using the discharge date minus the admission date plus 1 day
- Imputation methodology was used for missing admission or discharge dates (<1% of data)
- Hospitalizations were linked to confirmed or probable adjudicated AIDS-defining illness (ADI) or death (reviewed by an independent adjudication panel)

Inpatient costs per day

- Published estimates of daily hospital costs were taken from two studies of resource utilization in hospitalized HIV patients[1,2]
- Estimates were inflated to 2006 costs (US$) using the Medical Care consumer price index (CPI), providing an overall range of $1308–$2441
- Annual inpatient costs per patient were calculated by multiplying the number of inpatient days observed during the 48-week DUET study period by the range of costs per day

[1]Bozzette SA, et al. NEJM 2001;344:817–23
[2]Schackman BR, et al. Med Care 2006;44:990–7

Statistical analyses

- Negative binomial regression analyses were used to evaluate the rate of hospitalization events and the rate of total duration of hospitalization events over the period of hospitalization risk for each patient
- Variables tested were age, ethnicity, gender, HIV risk group, baseline CD4 cell count, baseline viral load, number of sensitive ARVs in the BR, ENF use, and clinical stage of HIV infection
- All univariate and mulitvariate models contained treatment group and study ID
- Factors from the univariate modeling, significant at the p=0.20 level, were included in an initial multivariate model
- Backwards selection was performed with the final multivariate model retaining factors significant at the p=0.10 level
- Incidence rate ratios (IRR) were calculated for variables relative to the reference category in both univariate and multivariate models

Patient demographics

Parameter, n (%)*	ETR + BR (n=599)	Placebo + BR (n=604)	Total (n=1203)
Median age (range), years	46 (18–77)	45 (18–72)	45 (18–77)
<40	111 (18.5)	116 (19.2)	227 (18.9)
40–49	310 (51.8)	300 (49.7)	610 (50.7)
≥50	178 (29.7)	188 (31.1)	366 (30.4)
Gender			
Female	60 (10.0)	69 (11.4)	129 (10.7)
Male	539 (90.0)	535 (88.6)	1074 (89.3)
Race/ethnicity			
Black	70 (13.2)	70 (13.0)	140 (13.1)
Hispanic	60 (11.3)	66 (12.2)	126 (11.8)
White	373 (70.1)	376 (69.8)	749 (69.9)
Oriental/Asian	7 (1.3)	3 (0.6)	10 (0.9)
Other	22 (4.1)	24 (4.5)	46 (4.3)
Not allowed to ask	67	65	132
HIV risk factor			
MSM	309 (66.3)	389 (64.4)	786 (65.3)
HET	137 (22.9)	158 (26.2)	295 (24.5)
IDU	28 (4.7)	23 (3.8)	51 (4.2)
MSM-IDU	2 (0.3)	9 (1.5)	11 (0.9)
HET-IDU	4 (0.7)	5 (0.8)	9 (0.7)
Other	31 (5.2)	20 (3.3)	51 (4.2)

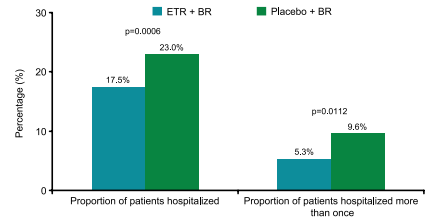
MSM = men who have sex with men; HET = heterosexual; IDU = injection drug use
*Except when median values are indicated

Clinical characteristics

Parameter, n (%)*	ETR + BR (n=599)	Placebo + BR (n=604)	Total (n=1203)
Baseline CD4 count (cells/mm^3)			
Median	99	109	105
<50	213 (35.6)	209 (34.7)	422 (35.1)
50–199	208 (34.8)	208 (34.5)	416 (34.6)
200–350	119 (19.9)	125 (20.7)	244 (20.3)
>350	58 (9.7)	61 (10.1)	119 (9.9)
Baseline HIV-1 RNA (copies/mL)			
Median	67 300	68 150	67 500
<1000	2 (0.3)	3 (0.5)	5 (0.4)
1000–29 999	163 (27.2)	171 (28.3)	334 (27.8)
30 000–100 000	206 (34.4)	213 (35.3)	419 (34.8)
>100 000	228 (38.1)	217 (35.9)	445 (37.0)
ENF use			
De novo	153 (25.5)	159 (26.3)	312 (25.9)
Not used	327 (54.6)	322 (53.3)	649 (53.9)
Reused	119 (19.9)	123 (20.4)	242 (20.1)
Stage of infection			
A	126 (21.0)	129 (21.4)	255 (21.2)
B	127 (21.2)	116 (19.2)	243 (20.2)
C	346 (57.8)	359 (59.4)	705 (58.6)
No. of sensitive ARVs			
0	101 (17)	97 (15.2)	198 (16.6)
1	217 (36.5)	231 (38.7)	448 (37.6)
2	160 (26.9)	166 (27.8)	326 (27.3)
≥3	117 (19.7)	103 (17.3)	220 (18.5)

*Except when median values are indicated

Hospitalization rate



- Over the 48-week study period, hospitalization rates were significantly lower for ETR than for placebo patients
- Fewer patients in the ETR than in the placebo group had more than one admission during the study interval

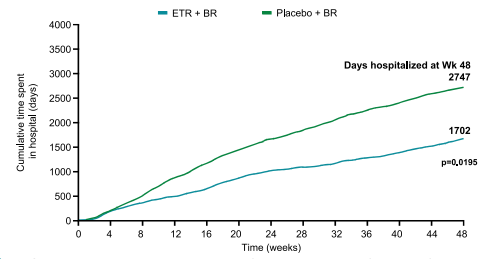
Hospitalization rates stratified by baseline CD4 cell count

CD4 cell count category	Total no. hosp.	Hosp. rate/ 100 pt yrs	Rate of hosp. due to ADI/ 100 pt yrs	Rate of hosp. patients who died/100 pt yrs	No. days hosp. in 48 weeks	Est. cost ($)* of hosp. days
ETR + BR						
Overall (n=599)	155	31.1	5.2	2.0	1702	2 226 216
<50 (n=213)	77	45.9	5.4	4.2	975	1 275 300
50–199 (n=208)	48	27.1	5.6	0.6	429	561 132
≥200 (n=177)	30	19.6	4.6	1.3	298	389 784
Placebo + BR						
Overall (n=604)	223	45.2	12.1	4.0	2747	3 593 076
<50 (n=209)	135	84.3	28.1	8.7	1886	2 466 888
50–199 (n=208)	43	24.8	3.5	2.9	517	676 236
≥200 (n=186)	45	28.2	5.6	0.6	344	449 952

- In both treatment groups, with the exception of the CD4 cell count <50 cells/mm^3 category in the placebo group, the rate of hospitalization due to ADIs was low and comparable between ETR and placebo
- There is a clear benefit for ETR versus placebo in the CD4 cell count <50 cells/mm^3 category

Hosp = hospitalization(s); pt yrs = patient years; *Calculated by multiplying the number of hospital days by the lower end of the range of cost of hospitalization ($1308; 2006 values)

Cumulative hospital days over 48 weeks



- Over the 48-week study period, the total number of days in hospital was significantly lower for ETR than for placebo patients

Predictors of rate of hospitalization and/or length of hospital stay

Patient characteristic	Overall hospitalization rates IRR (95% CI)	Overall hospitalization rates Adjusted IRR (95% CI)	No. days hospitalized IRR (95% CI)	No. days hospitalized Adjusted IRR (95% CI)
Baseline CD4 count (cells/mm^3)				
<50	3.15 (2.18–4.56)	2.86 (1.97–4.16)	2.68 (1.85–3.90)	2.06 (1.37–3.08)
50–199	1.12 (0.75–1.68)	1.09 (0.73–1.62)	1.81 (1.17–2.80)	1.57 (1.01–2.42)
≥200	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
No. active ARVs*				
0	2.42 (1.47–3.99)	1.86 (1.14–3.04)	2.37 (1.43–3.95)	1.66 (0.99–2.77)
1	1.29 (0.83–2.01)	1.10 (0.71–1.70)	1.90 (1.19–3.04)	1.53 (0.96–2.43)
2	1.14 (0.71–1.82)	1.11 (0.70–1.77)	1.26 (0.77–2.06)	0.99 (0.61–1.62)
≥3	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Clinical stage of infection				
Stage A/B	1.0 (Ref)	–	1.0 (Ref)	1.0 (Ref)
Stage C	1.48 (1.06–2.03)		1.90 (1.39–2.61)	1.60 (1.14–2.24)
Treatment group				
ETR	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Placebo	1.51 (1.11–2.06)	1.47 (1.09–1.98)	0.91 (0.67–1.25)	0.93 (0.69–1.25)

- Decreased CD4 cell count and no active ARVs in the BR were associated with increased hospitalization rates and length of stay; advanced clinical state was associated with increased length of stay; ETR use was associated with reduced hospitalization rate
- Age, ethnicity, gender, HIV risk group, baseline HIV-RNA and ENF use were not associated with increased hospitalization rate or length of stay (data not shown)

*As assessed by Phenotypic Sensitivity Score (PSS), ETR use was excluded

Hospitalization costs

- Using the 2006 Medical Care CPI 2006 cost estimates in US$ of $1308–$2441 per day, hospital costs were estimated for the overall cohort of patients in DUET at
  - $2.2–$4.2 million for ETR + BR
  - $3.6–$6.7 million for placebo + BR
- Estimated savings in hospital costs for the ETR + BR arm versus placebo arm
  - $1.4–$2.5 million

Conclusions

- Pooled 48-week data from the DUET trials show that ETR + BR provided a statistically significant reduction in overall hospitalization rate and days hospitalized versus placebo + BR.
- Baseline CD4 cell count, number of active ARVs in the BR and clinical stage of infection were found to be significant predictors of rate of hospitalization and/or length of hospital stay.
- Hospital costs were calculated to be lower for ETR + BR than placebo + BR.

Implications of the study

- Although long-term overall healthcare costs associated with ETR still need to be determined, this analysis suggests there is both a clinical and cost benefit for the use of ETR as part of a HAART regimen.
- Results from this analysis suggest that ETR use may be most useful in helping to reduce inpatient hospitalization in patients with low CD4 cell counts (<50 cells/mm^3).
- This study suggests potential hospital cost savings of more than US$1 million for patients in the ETR group.
- Future cost analyses are required to calculate the actual per patient saving; current data suggest decreases in hospitalization rates observed when ETR is added to HAART may be associated with a decrease in cost of care.
- Payers should consider these results when approving ARV drugs for use in HAART.

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DUET-1

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DUET-2

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