Health-Related Quality of Life (HRQoL) Improvement in Antiretroviral (ARV) Naïve HIV-infected Patients on Atazanavir or Lopinavir With Ritonavir Regimens: Week 24 Results From the CASTLE Study

Bristol-Myers Squibb
POSTER # TUPE0060

J. Su, J. Absalon, M. Mancini, U. Iloeje, D. McGrath, for the CASTLE Study Group
Bristol-Myers Squibb, Wallingford, CT, USA

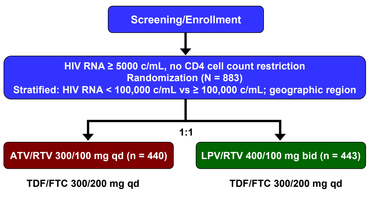
Jun Su
Bristol-Myers Squibb
Research Parkway
Wallingford, CT 06492
E-mail: jun.su@bms.com

BACKGROUND

Introduction

- Gastrointestinal (GI) tolerability is an important component of HRQoL, and an important factor impacting adherence and virologic failure among patients treated with protease inhibitor (PI)-based highly active antiretroviral therapy (HAART).[1]
- Atazanavir (ATV) is a potent, generally well-tolerated, once-daily HIV-1 PI extensively studied in treatment-naïve and treatment-experienced patients.
- The CASTLE study (**C**omparing the **A**ntiviral **E**fficacy and **S**afety of **A**tazanavir/ritonavir with **L**opinavir/ritonavir, Each in Combination With Fixed-Dose Tenofovir-**E**mtricitabine in HIV-1–Infected Treatment-Naïve Subjects) is an on-going 96-week, randomized, open-label, prospective, international, multicenter study comparing once-daily ATV/ritonavir (RTV) with twice-daily lopinavir (LPV)/RTV, both in combination with fixed-dose tenofovir (TDF)/emitricitabine (FTC) in 883 patients (**Figure 1**).

Figure 1. CASTLE Study Design[2]



Objective

- The objective of this substudy of CASTLE was to assess the impact of GI complications using the Irritable Bowel Syndrome (IBS) HRQoL questionnaire.

Methods

- HRQoL end points were assessed using the IBS-QoL questionnaire for treated patients with adequate linguistic skills and an evaluable number of items answered at baseline and at Week 24 (≥ 28/34 items answered).
- End points were assessed at baseline and Weeks 4, 12, and 24. The questionnaire consists of 34 items and derives an overall score and 8 subscale scores:
  - Dysphoria
  - Interference with activity
  - Body image
  - Health worry
  - Food avoidance
  - Social reaction
  - Sexual
  - Relationships
- Final scores were transformed to a 0 to 100 scale representing the lowest and highest possible scores; higher scores indicated a better IBS-related QoL.
- The summary scores, subscale scores, and changes from baseline were summarized over time.
- Categories for IBS-QoL change from baseline were:
  - Improvement (≥ 2-point positive change from baseline).
  - No change (< 2-point change from baseline [positive or negative]).
  - Worsening (≥ 2-point negative change from baseline).
- Principal analyses summarized changes from baseline in IBS-QoL overall score through Week 24. Post hoc analyses assessed categories of overall score change from baseline.
- Occurrence of GI adverse events (AEs) (diarrhea, nausea, vomiting) collected in the study through Week 24 for patients with evaluable IBS-QoL at baseline and at Week 24 are also presented.

RESULTS

- For subjects with evaluable IBS-QoL questionnaires at baseline, the median patient age was 35 years and 71% were men.
- Baseline HIV RNA levels and CD4 counts were similar in both treatment groups:
  - Median HIV RNA was 5.02 $\log_{10}$ c/mL and median CD4 was 210 cells/mm^3.
- A total of 599 patients had evaluable IBS-QoL questionnaires at baseline and Week 24.
- Disease characteristics were consistent between treatment regimens in the as-treated patient population (**Table 1**).

Table 1. HIV RNA and CD4 Count of Patients With Evaluable IBS-QoL Questionnaires at Baseline (As-treated Patients)

Baseline Value	ATV/RTV n = 343	LPV/RTV n = 349	Total N = 692
HIV RNA level ($\log_{10}$ c/mL), median	5.06	4.99	5.02
HIV RNA distribution (c/mL), n (%)			
< 30,000	74 (22)	77 (22)	151 (22)
30,000 – < 100,000	84 (24)	102 (29)	186 (27)
100,000 – < 500,000	143 (42)	135 (39)	278 (40)
≥ 500,000	42 (12)	35 (10)	77 (11)
CD4 cell count (cells/mm^3), median	208	211	210

- The IBS-QoL questionnaire was administered at baseline to 82% and 84% of patients on the ATV/RTV and LPV/RTV regimens, respectively.
- At Weeks 4, 12, and 24 the questionnaire administration rates were similar (range 80%-83%).
  - The predominant reason that the IBS-QoL was not completed was that the questionnaire was not available in the appropriate language.

Overall IBS-QoL Scores Through Week 24

- Most patients receiving the ATV/RTV regimen showed an increase in overall IBS-QoL scores throughout the study (**Figure 2**).
- Most patients receiving the LPV/RTV regimen had a decrease in overall IBS-QoL scores at Week 4, but their scores increased in Weeks 12 and 24 (**Figure 2**).

Figure 2. Mean Change in Overall IBS-QoL Score From Baseline to Week 24 in As-treated Patients

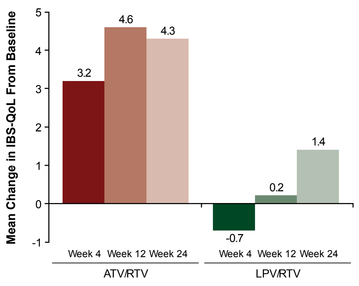


Table 2. IBS-QoL Mean Score Changes in Subscales From Baseline to Week 24 in As-treated Patients With Evaluable Data

	Mean Change (SE) From Baseline					
	Week 4		Week 12		Week 24	
	ATV/RTV n = 306	LPV/RTV n = 316	ATV/RTV n = 301	LPV/RTV n = 310	ATV/RTV n = 290	LPV/RTV n = 289
Dysphoria	3.3 (0.79)	-0.1 (0.75)	4.7 (0.79)	1.2 (0.94)	4.4 (0.84)	1.8 (0.97)
Interference with activity	3.1 (0.86)	-1.9 (0.79)	5.1 (0.83)	-0.4 (0.96)	4.4 (0.92)	0.0 (1.04)
Body image	1.6 (0.71)	-1.3 (0.68)	2.1 (0.69)	-0.1 (0.85)	1.8 (0.80)	1.1 (0.84)
Health worry	6.0 (0.96)	2.0 (0.99)	7.9 (1.02)	3.6 (1.23)	7.5 (0.99)	5.3 (1.18)
Food avoidance	4.0 (1.03)	-1.7 (1.07)	5.6 (0.95)	-0.6 (1.25)	5.6 (1.14)	0.4 (1.29)
Social reaction	1.9 (0.76)	-0.8 (0.71)	3.3 (0.73)	-0.4 (0.95)	3.2 (0.80)	0.4 (0.92)
Sexual	3.7 (1.06)	-0.1 (1.02)	4.7 (1.11)	-0.4 (1.19)	4.3 (1.20)	0.8 (1.15)
Relationships	1.2 (0.72)	-0.6 (0.75)	3.5 (0.75)	0.0 (0.99)	3.3 (0.89)	1.2 (1.00)

- Relative to baseline IBS-QoL values:
  - Patients who received the ATV/RTV-based regimen had increases in all subscales at each time point.
  - All mean subscale scores, with the exception of health worry, decreased at Week 4 in patients who received the LPV/RTV-based regimen.
  - At Week 12, all mean subscale scores, with the exception of dysphoria, health worry, and relationships had decreased in the LPV/RTV-treatment group.
  - By Week 24, all mean subscale scores for patients who received LPV/RTV had increased.

Worsening, No Change, and Improvements in IBS-QoL Scores

- Fewer patients in the ATV/RTV-treatment group than in the LPV/RTV-treatment group were in the worsening category at Weeks 4, 12, and 24 (**Table 3**).
- The percentage of patients that showed no change in IBS-QoL was similar in both treatment groups (range 42%-47%).
- More patients in the ATV/RTV-treatment group had improvements in overall IBS-QoL scores at Week 24 than at any other time point.
- More patients with a baseline CD4 count of 50 to < 200 cells/mm^3 in the ATV/RTV-treatment group had improvements in IBS-QoL scores than did those in the LPV/RTV-treatment arm (**Table 4**).

Table 3. Percentage of Patients Receiving ATV/RTV or LPV/RTV Regimens With a Worsening, No Change, or Improving IBS-QoL Score at Weeks 4, 12, and 24

	IBS-QoL Overall Score Change From Baseline							
	ATV/RTV				LPV/RTV			
	Baseline n = 335	Week 4 n = 306	Week 12 n = 301	Week 24 n = 290	Baseline n = 342	Week 4 n = 316	Week 12 n = 310	Week 24 n = 289
% Worsening	NA	17	15	16	NA	32	26	25
% No change	NA	47	45	42	NA	42	43	42
% Improving	NA	36	41	42	NA	26	31	34

Worsening, ≥ 2-point negative change from baseline; No change, <2-point change from baseline (positive or negative); Improving, ≥ 2-point positive change from baseline; NA, not applicable.

Table 4. Patients Receiving ATV/RTV or LPV/RTV Regimens With a Worsening, No Change, or Improving IBS-QoL Score at Weeks 4, 12, and 24 with a CD4 Cell Count < 50 cells/mm^3, 50 to < 200 cells/mm^3 or ≥ 200 cells/mm^3

	IBS-QoL Score Change From Baseline							
	ATV/RTV Number in Category/ Number Evaluable (%)				LPV/RTV Number in Category/ Number Evaluable (%)			
	Baseline	Week 4	Week 12	Week 24	Baseline	Week 4	Week 12	Week 24
Baseline CD4 cell count < 50 cells/mm^3	n = 43				n = 34			
Worsening	NA	5/37 (14)	4/38 (11)	6/34 (18)	NA	8/28 (29)	4/22 (18)	4/21 (19)
No change	NA	20/37 (54)	16/38 (42)	15/34 (44)	NA	12/28 (43)	10/22 (45)	6/21 (29)
Improving	NA	12/37 (32)	18/38 (47)	13/34 (38)	NA	8/28 (29)	8/22 (36)	11/21 (52)
Baseline CD4 cell count 50 to < 200 cells/mm^3	n = 116				n = 128			
Worsening	NA	17/105 (16)	14/103 (14)	11/96 (11)	NA	34/118 (29)	27/118 (23)	24/110 (22)
No change	NA	49/105 (47)	47/103 (46)	42/96 (44)	NA	48/118 (41)	45/118 (38)	40/110 (36)
Improving	NA	39/105 (37)	42/103 (41)	43/96 (45)	NA	36/118 (31)	46/118 (39)	46/110 (42)
Baseline CD4 cell count ≥ 200 cells/mm^3	n = 178				n = 185			
Worsening	NA	30/158 (19)	26/154 (17)	27/155 (17)	NA	57/168 (34)	49/168 (29)	42/156 (27)
No change	NA	73/158 (46)	69/154 (45)	65/155 (42)	NA	72/168 (43)	79/168 (47)	73/156 (47)
Improving	NA	55/158 (35)	59/154 (38)	63/155 (41)	NA	39/168 (23)	40/168 (24)	41/156 (26)

Worsening, ≥ 2-point negative change from baseline; No change, <2-point change from baseline (positive or negative); Improving, ≥ 2-point positive change from baseline; NA, not applicable.

GI Adverse Events

- Through Week 24, 7% (20/299) of ATV/RTV-treated patients compared with 15% (46/300) of LPV/ATV-treated patients had grade 2 to 4 treatment-related GI AEs (P = 0.001).
- No new or unexpected safety events were reported in the study.
- AEs were not treatment-limiting in most cases.

Concomitant GI Medication

- To assess whether increases in mean subscale scores in the LPV/RTV-treatment group at Week 24 were due to patients taking GI medication, the number of patients taking concomitant GI medications was analyzed.
- Of those patients who had evaluable IBS-QoL data at baseline and Week 24, fewer patients in the ATV/RTV-treatment group took concomitant GI medications:
  - 16 of 299 ATV/RTV-treated patients took concomitant GI medication.
  - 45 of 300 LPV/RTV-treated patients took concomitant GI medication.

CONCLUSIONS

- More ATV/RTV patients had improvements in IBS-QoL scores than did LPV/RTV patients.
  - The magnitude of improvement in the LPV/RTV-treatment group was less than that in the ATV/RTV-treatment group.
- ATV/RTV treatment resulted in fewer GI AEs than did LPV/RTV treatment. More than twice the number of patients taking LPV/RTV than those taking ATV/RTV required the use of antidiarrheal medications for GI toxicity.
- The difference in IBS-QoL score reductions between ATV/RTV and LPV/RTV was most pronounced early in treatment in patients with low CD4 counts.

REFERENCES

1. Carr A, Amin J. Presented at: 15th Conference on Retrovirus and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA.
2. Molina JM, et al. Presented at: 15th Conference on Retrovirus and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA.