Efficacy and Safety of Boosted Once-Daily Atazanavir and Twice-Daily Lopinavir Regimens in Treatment-Naïve HIV-1 Infected Subjects
CASTLE: 48-Week Results

Bristol-Myers Squibb

Presentation #37

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ABSTRACT

Background

- ATV/r is as effective as LPV/r with more favorable lipid and GI profiles in treatment-experienced HIV-infected patients. Comparative data in ARV-naive patients are needed.

Methods

- CASTLE is a randomized, open-label, multicenter, ongoing 96-week study to assess non-inferiority (10% margin) of ATV/r 300 mg/100 mg once-daily (QD) versus LPV/r 400 mg/100 mg twice-daily, both in combination with fixed-dose TDF 300 mg/FTC 200 mg QD, in treatment-naïve patients. The primary end point was the proportion of patients with HIV RNA < 50 c/mL at week 48; planned secondary assessments included percent with HIV RNA < 400 c/mL, CD4 cell count change, and safety.

Results

- 883 patients randomized, 878 treated. Baseline (BL) demographics and characteristics were well balanced. Median CD4 205 cells/mm^3; median plasma HIV RNA 4.98 $\log_{10}$ c/mL.

			Difference Estimate (95% CI) (ATV/r – LPV/r)
CVR[a]	**n = 440**	**n = 443**	
% < 50 c/mL	78	76	1.7 (-3.8, 7.1)
% < 400 c/mL	86	82	3.3 (-1.5, 8.1)
CVR[a], Baseline CD4 < 50 cells/mm^3	**n = 58**	**n = 48**	
% < 50 c/mL	78	63	
Fasting Lipid Mean % Δ from BL at 48 weeks[b]	**n = 421**	**n = 415**	
Total cholesterol (TC)	12	24	-9.5 (-11.8, -7.0)[c]
LDL	12	15	-2.9 (-7.1, 1.5)
HDL	27	32	-3.8 (-7.8, 0.3)
Non-HDL	7	21	-11.6 (-14.5, -8.7)[c]
TG	13	51	-25.2 (-29.8, -20.2)[c]

[a] Confirmed Virologic Response (ITT), Non-Completers = Failure
[b] Last Observation Carried Forward
[c] $P < 0.0001$

- At week 48, mean CD4 increases from BL for ATV/r and LPV/r were 203 and 219 cells/mm^3, respectively. Fewer patients on ATV/r (2%) than LPV/r (7%)* initiated lipid lowering therapy. The proportion of patients with a TC:HDL ratio > 5 at week 48 was 12% and 20% on ATV/r and LPV/r, respectively. Patients on ATV/r had a lower incidence of grade 2-4 treatment-related diarrhea (2% vs 11%) and nausea (4% vs 8%) than LPV/r. Grade 3-4 ALT/AST elevations were low (≤ 2%) in both arms. Discontinuations prior to week 48 were: ATV/r, 9%; LPV/r, 13%. AE-related discontinuations were 2% and 3% on ATV/r and LPV/r, respectively. Three patients (< 1%) discontinued ATV/r due to jaundice/hyperbilirubinemia.

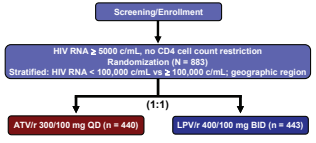
Conclusions

- In treatment-naive patients, ATV/r demonstrated similar efficacy, a lower incidence of GI-related AEs, and a significantly better lipid profile (TC, TG, non-HDL) compared to LPV/r. In combination with TDF and FTC, both ATV/r and LPV/r were generally well tolerated with few discontinuations through 48 weeks.

*Original submitted abstract stated 8%, correct value is 7%.

STUDY DESIGN

- International, multicenter, open-label, randomized, 96-week study to determine the comparative clinical efficacy and safety of ATV/r and LPV/r in treatment-naive HIV-1 infected subjects



STUDY OBJECTIVES

Primary End Point

- Proportion of subjects with HIV RNA < 50 c/mL at week 48
  - Principal analysis: ITT-Confirmed Virologic Response (CVR) - (NC = F)
  - Supportive analyses:
    - ITT-TLOVR
    - On-treatment-Virologic Response Observed Cases (OT-VROC)

Primary Objective

- Demonstrate noninferiority of ATV/r once daily vs LPV/r twice daily based on primary end point
  - Δ -10%, ATV/r - LPV/r

Secondary End Points

- Immunologic response
- Safety and tolerability
- Changes in fasting lipids

RESULTS

Baseline Characteristics

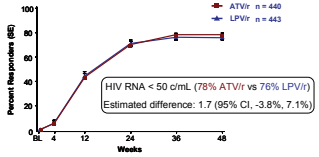
	ATV/r n = 440	LPV/r n = 443
Age, median (min-max)	**34** (19-72)	**36** (19-71)
Female, n (%)	**138** (31)	**139** (31)
CDC Class C AIDS, n (%)	**19** (4)	**24** (5)
HIV RNA $\log_{10}$ c/mL, median (min-max)	**5.01** (2.60-5.88)	**4.96** (3.32-5.88)
HIV RNA ≥ 100,000 c/mL, n (%)	**225** (51)	**208** (47)
CD4 cells/mm^3, median (min-max)	**205** (2-794)	**204** (4-810)
CD4 < 50 cells/mm^3, n (%)	**58** (13)	**48** (11)
Hepatitis B and/or C co-infection, n (%)	**61** (14)	**51** (12)

Disposition

	ATV/r n = 440 n (%)	LPV/r n = 443 n (%)
Randomized	**440**	**443**
Treated	**438** (99)	**440** (99)
Discontinued before week 48	**39** (9)	**58** (13)
AEs	**10** (2)	**14** (3)
Death	**4** (< 1)	**4** (< 1)
Lack of efficacy	**5** (1)	**8** (2)
Lost to follow-up	**6** (1)	**6** (1)
Poor/noncompliance	**6** (1)	**9** (2)
Withdrew consent	**4** (< 1)	**13** (3)
Other (pregnancy, no longer meets study criteria, other)	**4** (< 1)	**4** (< 1)

RESULTS

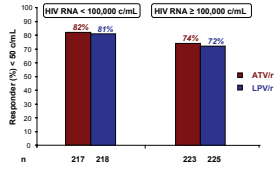
Primary Efficacy End Point — ITT-Confirmed Virologic Response (NC = F)



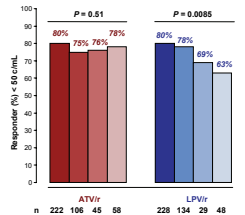
ATV/r has noninferior antiviral efficacy compared with LPV/r

Supporting Analyses:
ITT-TLOVR: HIV RNA < 50 c/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)
OT-VROC: HIV RNA < 50 c/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

ITT-Confirmed Virologic Response (NC = F) by Qualifying HIV Viral Load



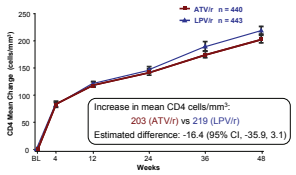
Response Rate by Baseline CD4 Cell Count — Post Hoc Analysis



P-values are from Cochran-Armitage trend test

RESULTS

CD4 Mean Change



Adverse Events Summary

		ATV/r n = 441 n (%)	LPV/r n = 437 n (%)
Serious Adverse Events (SAEs)		**51** (12)	**42** (10)
All grade 2-4 treatment-related AEs[a]		**115** (26)	**129** (30)
Grade 2-4 treatment-related AEs ≥ 3%[a,b]	Jaundice	**16** (4)	**0**
	Nausea	**17** (4)	**33** (8)
	Diarrhea	**10** (2)	**50** (11)
	Rash	**14** (3)	**9** (2)

[a]Through 48 weeks
[b]Excluding laboratory abnormalities reported as AEs

- Renal all grade AEs: 2% in both arms
- 1 discontinuation due to renal AE in each arm

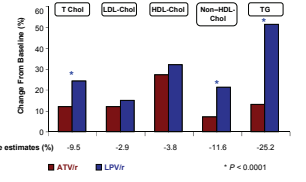
Selected Grade 3-4 Laboratory Abnormalities

	ATV/r n = 441 n (%)	LPV/r n = 437 n (%)
Total bilirubin elevation (> 2.5 × ULN)	**146** (34)	**1** (<1)
ALT elevation (> 5 × ULN)	**8** (2)	**6** (1)
AST elevation (> 5 × ULN)	**9** (2)	**2** (<1)
Total cholesterol (≥ 240 mg/dL)	**30** (7)	**77** (18)
Triglycerides (≥ 751 mg/dL)	**2** (<1)	**15** (4)
Hyperglycemia (≥ 251 mg/dL)	**1** (<1)	**1** (<1)

- Change from baseline at 48 weeks in renal function
  - Mean serum creatinine: + 0.05 mg/dL ATV/r, + 0.02 mg/dL LPV/r
  - Median calculated creatinine clearance: 1% decrease in both arms

RESULTS

Fasting Lipids Mean Percent Changes From Baseline (LOCF)



- 2% of ATV/r vs 7% of LPV/r subjects initiated lipid-lowering therapy during the study

CONCLUSIONS

- Once-daily ATV/r demonstrated comparable antiviral efficacy to twice-daily LPV/r, both in combination with TDF/FTC, in treatment-naïve patients
- In patients with advanced disease, ATV/r was highly effective in achieving virus undetectability
- Both regimens were generally well-tolerated with low rates of discontinuation
  - Jaundice and hyperbilirubinemia were more commonly reported for ATV/r
  - Nausea and diarrhea occurred with greater frequency on LPV/r
- ATV/r had a significantly better lipid profile (TC, TG, non-HDL) compared to LPV/r
- Once-daily ATV/r plus TDF/FTC is an appropriate therapeutic option for treatment-naïve patients

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