ACTHIV11

Pitavastatin 4 mg Superior to Pravastatin 40 mg on LDL-C Reduction after 12 and 52 Weeks of Treatment in Patients with HIV Infection and Dyslipidemia with and without Ritonavir-based Therapy

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BACKGROUND

- Approximately 35 million people worldwide are currently living with HIV/AIDS, including 2.2 million in Europe and 1.2 million in the United States (US).[1-3]
- Dyslipidemia is a common comorbidity in adults with HIV-1 infection. In the US, for example, dyslipidemia has been reported in 81% of men (median age 47 yrs) and 67% of women (median age 45 yrs) with HIV-1 infection.[4]
- Contributing factors include the HIV infection itself as well as antiretroviral (ARV) therapy.[5] The most deleterious changes in lipid levels are seen with ARV combinations that include protease inhibitors (PIs).[6]
- Statins are the most effective agents for reducing LDL-C.[7]
- Some statins and PIs have contraindications or dosing restrictions because of the shared metabolic pathway, cytochrome P450 (CYP) 3A4.[7,8]
- Ritonavir is a potent inhibitor of CYP 3A4, and is used to "boost" the activity of other PIs.[7]
- The drug-drug interaction between certain statins and PIs can result in elevated statin levels, which lead to an increased risk for muscle-related adverse events (e.g., mylagia or rhabdomyolisis).[7]
- Neither pitavastatin nor pravastatin depend on the CYP enzyme system for their metabolism,[7] and neither agent has dose limitations or contraindications when co-administered with PIs, according to the recent FDA safety communication.[8]
- In adults with dyslipidemia, including those with comorbid HIV infection in the INTREPID (**HI**V-infected patie**N**ts and **TRE**atment with **PI**tavastatin vs. pravastatin for **D**yslipidemia) trial, pitavastatin 4 mg has demonstrated significantly greater reductions in LDL-C vs. pravastatin 40 mg after 12 weeks[9-12] and 52 weeks[11,12] of treatment. Reductions in apolipoprotein B, non-HDL-C, and total cholesterol were also significantly greater for pitavastatin 4 mg.[9-12]
- The present pre-specified exploratory analysis from INTREPID evaluated the effect of concomitant ritonavir therapy on short- and long-term LDL-C reduction.

References

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Disclosures: C. Sponseller is an employee of Kowa Pharmaceuticals America, Inc.; S. Campbell is an employee of Kowa Research Institute, Inc.; V. Kryzhanovski is an employee of Lilly USA, LLC; J. Aberg was an INTREPID study investigator and is a consultant to Kowa Pharmaceuticals America, Inc.

Acknowledgments: Lorraine R. Baer, PharmD (Baer PharMed Consulting, Ltd.) for content development support.

OBJECTIVE

- To determine whether ritonavir use affects the reduction in LDL-C.

METHODS

Study Design

- INTREPID was a Phase 4, multicenter, 12-week, randomized, double-blind, double-dummy superiority study followed by a 40-week safety extension study (NCT01301066).
- There was a minimum 4-week washout/dietary stabilization period prior to randomization.
- Eligible subjects were randomized in a 1:1 ratio, stratified by the presence or absence of viral hepatitis B or C, to either pitavastatin 4 mg or pravastatin 40 mg. Dosing was once daily in the morning.
  - Pitavastatin 4 mg: subjects received 1 tablet of pitavastatin 4 mg + 1 placebo capsule.
  - Pravastatin 40 mg: subjects received 1 capsule of pravastatin 40 mg (2 tablets of pravastatin 20 mg overencapsulated) + 1 placebo tablet.
- Blood samples for determination of lipid parameters were drawn following an overnight fast.

Study Population

- Adults (18–70 yrs) with documented HIV infection and documented dyslipidemia.
- **Key inclusion criteria:**
  - ARV therapy for ≥6 months prior to randomization, with no change in regimen for ≥3 months prior to randomization.
  - HIV-1 RNA <200 copies/mL and CD4 cell count >200 cells/mm^3 for ≥3 months prior to randomization.
  - Fasting serum LDL-C of 130-220 mg/dL (inclusive) and triglycerides ≤400 mg/dL after the minimum 4-week washout/dietary stabilization period.
- **Key exclusion criteria:**
  - Use of darunavir
  - Presence of diabetes or cardiovascular disease

Endpoints

- **Primary:** Superiority of pitavastatin 4 mg vs. pravastatin 40 mg based on adjusted mean % change in fasting serum LDL-C from Baseline to Week 12.
- **Exploratory:** Effect of pitavastatin 4 mg and pravastatin 40 mg on LDL-C according to concomitant ritonavir use (either ongoing or with a start or end date after the first dose of study drug).

Statistical Analysis

- Analyses were conducted using the modified intention-to-treat (mITT) population, defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 on-treatment lipid assessment.
- A last observation carried forward (LOCF) methodology and an analysis of covariance (ANCOVA) model were used to determine % change in LDL-C as the dependent variable and treatment as the independent variable, after adjusting for site, viral hepatitis B/C infection status at randomization (Yes/No), and concomitant ritonavir use.
- For the ritonavir data, where data failed a test of normality, the treatments were compared using a nonparametric van Elteren test to confirm the ANCOVA conclusions; p-values were 2-sided and significance was tested.

RESULTS

Table 1. Baseline Demographics/Characteristics (All Randomized Subjects)

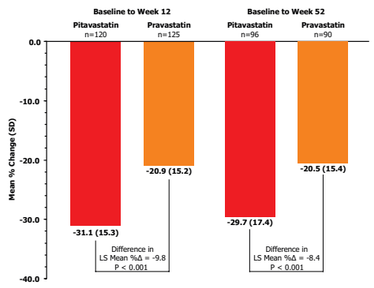
Demographic/ Characteristic	Pitavastatin 4 mg n=126	Pravastatin 40 mg n=126
Age, yrs	50.1 (7.5)	49.2 (8.7)
Males, n (%)	106 (84.1)	111 (88.1)
Race, n (%)		
Caucasian	107 (84.9)	96 (76.2)
African-American	16 (12.7)	23 (18.3)
Other	3 (2.4)	7 (5.6)
Ethnicity, Not Hispanic/Latino, n (%)	95 (75.4)	92 (73.0)
Body mass index, kg/m^2	27.2 (4.5)	28.2 (4.9)
Framingham 10-yr risk CHD assessment score, %	6.6 (5.1)	6.4 (4.8)
Duration of HIV, yrs	12.7 (7.7)	12.5 (7.2)
Hepatitis B or C, n (%)	12 (9.5)	13 (10.3)
CD4 cell count, cells/mm^3	648.5 (246.8)	563.7 (211.3)
HIV-1 RNA, log copies	1.2 (0.3)	1.1 (0.2)
Ritonavir use, n (%)	42 (33.3)	45 (35.7)

Data are mean (SD) unless otherwise noted.
Note: The study period was February 2011-March 2013; this study population falls outside the 4 major Statin Benefit groups according to the 2013 ACC/AHA cholesterol guidelines.

Table 2. LDL-C Measurements (mITT Population)

Study Visit	Pitavastatin 4 mg LDL-C, mean, mg/dL Ritonavir	Pitavastatin 4 mg LDL-C, mean, mg/dL No Ritonavir	Pravastatin 40 mg LDL-C, mean, mg/dL Ritonavir	Pravastatin 40 mg LDL-C, mean, mg/dL No Ritonavir
Baseline	n=39	n=82	n=45	n=81
	152.0	156.6	153.7	155.1
Week 12	n=38	n=82	n=45	n=80
	110.3	103.5	120.4	121.8
Week 52	n=34	n=62	n=33	n=57
	109.6	108.4	124.8	120.6

Figure 1. Primary Study Results: LDL-C: Mean Percent Change from Baseline to Week 12 and Week 52



- Pitavastatin 4 mg was superior to pravastatin 40 mg on LDL-C lowering at Week 12 (primary endpoint).

Figure 2. Week 12: Mean Percent Change from Baseline in LDL-C

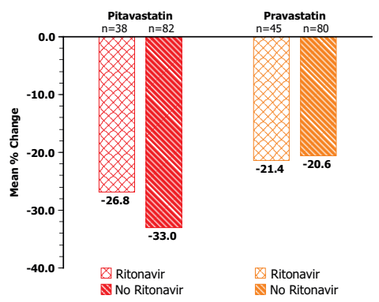
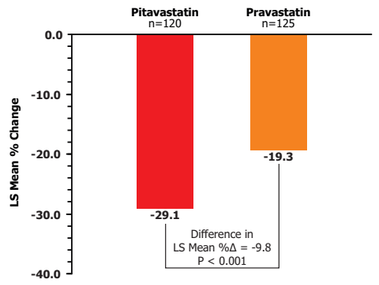


Figure 3. Week 12: Pitavastatin vs. Pravastatin in LDL-C Reduction (Adjusted for Site, Hepatitis B/C, and Ritonavir Use)



- The change from Baseline to Week 12 in LDL-C was statistically significant (P < 0.001) for each treatment.

Figure 4. Week 52: Mean Percent Change from Baseline in LDL-C

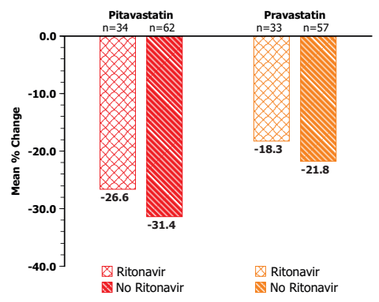
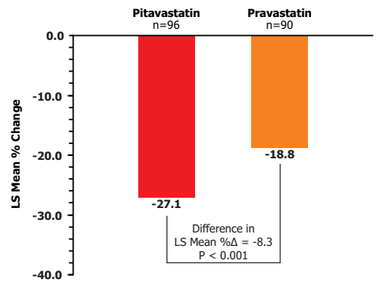


Figure 5. Week 52: Pitavastatin vs. Pravastatin in LDL-C Reduction (Adjusted for Site, Hepatitis B/C, and Ritonavir Use)



- The change from Baseline to Week 52 in LDL-C was statistically significant (P < 0.001) for each treatment.

Table 3. Selected Safety Parameters (52-week data)

	Pitavastatin 4 mg (n=126)	Pravastatin 40 mg (n=126)
	Number of Subjects (%)	
Treatment-Emergent Adverse Event (TEAE)		
Any TEAE	85 (67.5)	88 (69.8)
Treatment-related TEAE	16 (12.7)	12 (9.5)
Treatment-emergent serious adverse event	7 (5.6)	3 (2.4)
Deaths	0	0
Discontinuations due to TEAEs		
Any discontinuation due to TEAEs	6 (4.8)	5 (4.0)
Upper abdominal pain	2 (1.6)	0
Diarrhea	2 (1.6)	0
Blood creatine kinase increased	1 (0.8)	1 (0.8)
Nausea	1 (0.8)	1 (0.8)
Myalgia	1 (0.8)	1 (0.8)
Dizziness	1 (0.8)	0
Fatigue	1 (0.8)	0
Hyperhidrosis	1 (0.8)	0
Cerebrovascular accident	0	1 (0.8)
Muscular weakness	0	1 (0.8)
Most Common (occurring in >5% in either treatment group) TEAEs		
Diarrhea	12 (9.5)	4 (3.2)
Bronchitis	8 (6.3)	3 (2.4)
Nasopharyngitis	7 (5.6)	6 (4.8)
Headache	7 (5.6)	3 (2.4)
Upper respiratory tract infection	5 (4.0)	14 (11.1)
Sinusitis	4 (3.2)	10 (7.9)
Nausea	4 (3.2)	7 (5.6)
Musculoskeletal and Connective Tissue Disorders		
Back pain	4 (3.2)	4 (3.2)
Arthralgia	3 (2.4)	4 (3.2)
Pain in extremity	2 (1.6)	4 (3.2)
Myalgia	2 (1.6)	3 (2.4)
Virologic Status		
Virologic failure[a]	4 (3.2)	6 (4.8)

[a]Virologic failure was defined as an HIV-1 RNA value >200 copies/mL and a >0.3 log increase from baseline.

SUMMARY

- Pitavastatin 4 mg and pravastatin 40 mg significantly reduced LDL-C after 12 and 52 weeks of treatment, with or without ritonavir (ANCOVA, P<0.001).
- The reductions in LDL-C were significantly greater with pitavastatin — LS mean percent treatment differences: Week 12, -9.8%; Week 52, -8.3% — van Elteren, P<0.001.

CONCLUSIONS

- In the overall study population:
  - Pitavastatin 4 mg demonstrated a superior reduction in LDL-C compared with pravastatin 40 mg in HIV-infected adults with dyslipidemia at Week 12.
  - The reductions in LDL-C at Week 12 and Week 52 were significantly greater for pitavastatin 4 mg vs. pravastatin 40 mg.
- Use of ritonavir did not change the primary results of the study, i.e., pitavastatin reduced LDL-C significantly more than pravastatin after 12 and 52 weeks of therapy.
- Use of ritonavir does not affect the lipid-lowering effect of pitavastatin or pravastatin.

Poster presented at the American Conference for the Treatment of HIV, April 30-May 2, 2015, Dallas, TX (Encore poster, previously presented at the 20th International AIDS Conference (AIDS 2014), 20–25 July 2014, Melbourne, Australia.)

Research sponsored by Kowa Pharmaceuticals America, Inc. and Eli Lilly and Company.