+ SIM 10, 20, 40 or 80; or PBO. Primary efficacy endpoint was % reduction from baseline to endpoint in direct LDL-C for pooled EZE + SIM vs pooled SIM alone.

Results: Table shows mean % change from baseline to endpoint.

Treatment	Direct LDL-C	HDL-C	TG
PBO (n=70)	-1.3	+0.9	+2.4
EZE 10 mg (n=61)	-18.1	+5.1	-8.3
Pooled SIM (n=263)	-36.1	+6.9	-16.6
Pooled EZE + SIM (n=274)	-49.9*	+9.3*	-24.1*

*$P \leq 0.03$ for pooled EZE+SIM vs SIM

EZE + SIM significantly improved LDL-C, HDL-C and TG compared to SIM alone ($P<0.01$). EZE provided an added 13.8% LDL-C reduction, 2.4% HDL-C increase and 7.5% TG reduction compared to pooled SIM alone. EZE + SIM provided LDL-C reductions of 44-57%, TG reductions of 20-28% and HDL-C increases of 8-11% depending on the dose. EZE 10 mg + SIM 10 mg and SIM 80 mg alone each provided 44% LDL-C reduction. EZE + SIM was well tolerated, with a safety profile similar to PBO.

Conclusion: When co-administered with SIM, EZE provided significant incremental reductions in LDL-C and TG, as well as increases in HDL-C. The co-administration of EZE and SIM offers a highly efficacious new treatment approach to pts with hypercholesterolemia.

1084-91 Ezetimibe Co-Administered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia

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Background: Efficacy and safety of ezetimibe (EZE) administered with atorvastatin (ATV) in pts with primary hypercholesterolemia were assessed in a Phase III, multicenter, randomized, double-blind, placebo-controlled study.

Methods: After dietary stabilization on a NCEP Step I or stricter diet, a 2-12-wk screening/washout period and a 4-wk, single-blind, PBO lead-in period, 628 pts with baseline LDL-C ≥145 to ≤250 mg/dl + TG ≤350 mg/dl were randomized to 1 of the following administered daily for 12 consecutive wks: EZE 10 mg; ATV 10, 20, 40 or 80 mg; EZE 10 mg + ATV 10, 20, 40 or 80 mg; or PBO. Primary efficacy endpoint was % reduction from baseline to endpoint in direct LDL-C for pooled EZE + ATV vs pooled ATV alone.

Results: EZE + ATV was well tolerated, with a safety profile similar to ATV alone and to PBO. Table shows mean % change from baseline to endpoint.

Treatment	Direct LDL-C	HDL-C	TG
PBO (n=60)	5.9	3.7	4.4
EZE 10 mg (n=65)	-18.4	4.2	-3.4
Pooled ATV (n=248)	-42.4	4.3	-21.5
Pooled EZE + ATV (n=255)	-54.5*	7.3*	-29.5*

*$P<0.01$ for pooled EZE+ATV vs ATV

EZE + ATV significantly improved LDL-C, HDL-C and TG compared to ATV ($P<0.01$). EZE provided an added 12.1% LDL-C reduction, 3.0% HDL-C increase and an added 8.0% TG reduction vs pooled ATV. EZE + ATV provided LDL-C reductions of 50-60%. TG reductions of 26-35% and HDL increases of 4.6-9.2% depending on the dose. LDL-C reduction with EZE 10 mg + ATV 10 mg (50%) and ATV 80 mg alone (51%) was similar.

Conclusion: When co-administered with ATV, EZE provided significant incremental reductions in LDL-C and TG and increases in HDL-C. Co-administration of EZE and ATV offers a highly efficacious new treatment option for pts with hypercholesterolemia.

1084-92 Ezetimibe Significantly Reduces Low-Density Lipoprotein Cholesterol in Homozygous Familial Hypercholesterolemia

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Background: Current pharmacological agents for treatment of homozygous familial hypercholesterolemia (HoFH) have limited efficacy. We evaluated the efficacy, safety and tolerablity of ezetimibe (EZE), a novel selective cholesterol absorption inhibitor, in HoFH pts already taking atorvastatin (A) or simvastatin (S).

Methods: Fifty HoFH pts on diet and open-label 40 mg QD (A) or (S), with (n=25) or without (n=25) concomitant LDL apheresis, were randomized (double blind) to 1 of 3 daily 12-week treatments 1) A or S 80 mg, 2) EZE 10 mg + A or S 40 mg, or 3) EZE 10 mg+ A or S 80 mg. The primary comparison was mean % change in LDL-C from baseline to endpoint for the group receiving statins alone (Statin-80) vs the group receiving EZE + A or S at either dose (EZE+Statin-40/80). Mean % change in LDL-C for the group randomized to EZE + A or S 80 mg (EZE+Statin-80) was also compared to Statin-80.

Results: The table shows least square mean LDL-C concentrations.

Treatment	LDL-C (mg/dl)		% Change
	Baseline	Endpoint	(± SE)
Statin 80 (n=17)	339	319	-6.7 ± 4.2
EZE+Statin 40/80 (n=33)	313	247	-20.7 ± 3.2*
EZE+Statin 80 (n=17)	273	196	-27.5 ± 3.5*

*$P < 0.01$ vs. Statin-80 group

Similar and significant LDL-C reductions were observed for the subset of pts who had a genotypic diagnosis of HoFH (n=32). No significant between-group differences were observed for HDL-C or TG. EZE was well tolerated as determined by safety laboratory, adverse event, and drug discontinuation assessments.

Conclusion: EZE + A or S produced clinically important LDL-C lowering compared to best therapy with A and S in pts with HoFH. EZE provides a new, complementary pharmacological approach to this high-risk population.

1084-93 Does Cholesterol and/or Fat Intake Affect Plasma Lipid Efficacy of Ezetimibe?

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Objective: To assess effect of degree of dietary saturated fat and cholesterol restriction on efficacy of ezetimibe (EZE), a new selective cholesterol absorption inhibitor, in 1719 patients with primary hypercholesterolemia.

Methods: After 6-8 weeks instruction of NCEP Step I or stricter diet during the single-blind PBO lead-in, patients with plasma LDL-C 130-250 mg/dl and TG ≤350 mg/dl were randomized 3:1 to EZE 10 mg/d or PBO for 12 weeks in 2 identically designed Phase III, double-blind studies. Data from these 2 studies were pooled for analysis. Primary endpoint was % reduction of direct LDL-C from baseline to endpoint. Diet compliance was assessed every 2-6 weeks at a centralized center by computer analysis of 3-day food-intake records. A RISCC (Ratio of Ingested Saturated Fat and Cholesterol over Calories) score was used to quantitate all fat-related diet components and to compare diets between treatments. RISCC=(1.01[saturated fat in g] + 0.05[cholesterol in mg]) ÷ (total Kcal/1000).

Results: Of 1,719 patients (831 men, 888 women; ages 18-86 y), 1288 were randomized to EZE and 431 to PBO. Baseline characteristics were comparable between groups. The % change (mean ± SEM) in plasma lipid from baseline to endpoint was used to compare EZE and PBO patients in the 1st quartile (lowest) and 4th quartile (highest) of RISCC values (≤13, and ≥20) and dietary cholesterol (≤124, and ≥250 mg) at baseline. For EZE patients, % LDL-C reduction was -19 ± 0.6 and -19 ± 0.6 for patients in the 4th quartile of RISCC (n=353) or cholesterol (n=319), respectively, vs -16 ± 0.6 and -17 ± 0.6 for patients in the 1st quartile of RISCC (n=335) or cholesterol (n=300), respectively. For PBO, % LDL-C reduction was -1± 1 and -0.1 ± 1 for patients in the 4th quartile of RISCC (n=109) or cholesterol (n=95), respectively, vs -0.5 ± 1 and 0.1 ± 1 for patients in the 1st quartile of RISCC (n=114) or cholesterol (n=115), respectively. The % change LDL-C in the 1st and 4th quartiles was similar for EZE vs PBO.**Conclusions**: LDL-C lowering attributable to EZE for the lowest and highest quartiles of cholesterol or fat intake did not differ significantly.

1084-94 Atazanavir Plus Saquinavir Once Daily: Favorable Effects on Lipid Profiles in Patients Failing Prior Protease Inhibitor Therapy (Trial AI424-009)

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Background: Currently approved HIV-1 protease inhibitors (PIs) may increase risk for CV events by altering lipid metabolism. Atazanavir (BMS-232632) is a once-daily PI that rapidly and durably suppresses HIV RNA and increases CD4. Atazanavir does not increase total cholesterol (TC), low-density lipoprotein cholesterol (LDL), or triglyceride (TG) levels in antiretroviral-naïve subjects compared with prompt, marked, and sustained elevations with current PIs. Atazanavir and saquinavir have complementary resistance profiles and favorable PK interactions allowing for once-daily dosing of the combination. This protocol evaluated the safety, tolerability, and efficacy of dual PI therapy with atazanavir (400 or 600 mg qd)/saquinavir (1,200 mg qd) or ritonavir (400 mg bid)/saquinavir (400 mg bid) + 2 NRTIs after virologic failure on a PI regimen.

Methods: Randomized, active-controlled, blinded study in 85 adults with HIV RNA 1,000-100,000 c/mL and CD4 ≥ 100 cells/mm^3.

Results: Wk 24, Observed Data

	Atazanavir/saquinavir once daily		Ritonavir/saquinavir twice daily
	400 mg (n=34)	600 mg (n=28)	400 mg (n=23)
Median baseline, mg/dL (mean % change from baseline, n)			
TG	223 (-23, 15)	177 (-21, 13)	191 (90, 8)
TC	181 (-1, 27)	199 (-9, 20)	202 (10, 13)
Mean change from baseline (SE, n)			
HIV RNA ($\log_{10}$ c/mL)	-1.28 (0.20, 29)	-1.17 (0.20, 22)	-1.50 (0.31, 13)
CD4 (cells/mm^3)	55 (17, 29)	67 (18, 22)	98 (25, 13)

Updated results to wk 48 will be presented. **Conclusion:** In subjects failing a prior PI regimen, atazanavir/saquinavir lowered TC, LDL, and TG levels from baseline, whereas ritonavir/saquinavir produced substantial increases. Atazanavir/saquinavir was safe and well tolerated and showed significant antiviral effect at wk 24. The ability to improve serum lipid profiles in PI-experienced subjects suggests that atazanavir reduces risk factors for CV events in this population.