Calculated LDL-C: Individual Rx Groups: Mean % ΔBetween Baseline & Each Visit:

	Plac	Ez	All Statin	Ez + All Statin	Statin 10mg	Ez+ Statin 10 mg	Statin 20 mg	Ez+ Statin 20 mg	Statin 40 mg	Ez+ Statin 40 mg	Statin 80 mg	Ez+ Statin 80 mg
Lova:												
wk. 2	-0.8	-20.9	-26.5	-43.1	-21.7	-38.6	-26.0	-43.2	-31.9	-47.5	NA[a]	NA[a]
wk. 4	-1.6	-20.0	-28.6	-43.0	-22.2	-37.7	-29.6	-44.1	-34.1	-47.3		
wk. 8	-0.9	-20.2	-27.7	-42.8	-22.2	-38.1	-27.4	-41.3	-33.4	-48.9		
wk.12	+1.0	-18.6	-26.3	-41.7	-20.4	-35.1	-26.2	-43.1	-32.2	-46.9		
endpt.	+0.4	-18.7	-25.4	-40.4	-20.2	-34.2	-25.6	-40.8	-30.5	-46.1		
Simv												
wk. 2	-1.1	-20.0	-36.1	-52.5	-28.9	-45.7	-32.3	-49.3	-37.7	-55.1	-45.7	-60.1
wk. 4	+0.2	-20.5	-39.3	-54.1	-30.4	-46.7	-35.3	-50.9	-42.3	-57.2	-49.2	-61.8
wk. 8	-0.8	-19.5	-39.0	-53.0	-29.2	-46.4	-37.2	-48.9	-40.0	-54.8	-49.8	-61.8
wk.12	+0.4	-19.9	-38.3	-53.4	-28.9	-45.8	-38.1	-48.8	-39.1	-56.3	-47.1	-62.9
endpt	-1.5	-19.1	-36.5	-51.3	-27.2	-45.5	-36.5	-46.3	-37.5	-55.8	-44.7	-57.6
Prava												
wk. 2	-1.2	-19.5	-25.1	-41.4	-20.7	-37.3	-26.0	-40.7	-28.7	-46.3	NA[a]	NA[a]
wk. 4	-1.9	-20.0	-26.9	-43.2	-20.4	-39.4	-26.8	-42.3	-33.5	-47.8		
wk. 8	-2.6	-20.8	-26.3	-42.2	-22.6	-38.8	-26.1	-41.9	-30.2	-46.0		
wk.12	-0.5	-19.7	-26.1	-40.1	-21.3	-35.2	-25.2	-40.5	-31.9	-44.6		
endpt	-0.6	-19.6	-25.2	-38.6	-21.3	-33.8	-23.2	-39.7	-31.1	-42.4		
Atorv												
wk. 2	+3.0	-17.5	-42.0	-58.7	-35.2	-52.5	-38.3	-56.2	-45.0	-63.3	-49.6	-62.8
wk. 4	+2.0	-21.1	-45.5	-59.0	-38.5	-53.9	-41.9	-55.4	-48.1	-64.1	-53.6	-62.5
wk. 8	+3.6	-21.6	-45.1	-58.8	-37.0	-53.9	-41.1	-58.4	-48.6	-59.8	-53.7	-63.1
wk.12	+4.1	-20.7	-45.7	-57.7	-38.0	-54.7	-43.1	-55.8	-46.2	-57.6	-55.3	-62.8
endpt.	+4.3	-20.0	-44.2	-56.3	-36.5	-53.4	-41.8	-54.2	-44.8	-56.4	-53.8	-61.2

a= not applicable

Comments on the above table:

Overall, in each of the 4 factorial studies, efficacy was maintained over the 12-week treatment period for the reduction in LDL-C. The difference in the mean percent change in LDL-C from baseline to week 2 compared to that at endpoint was no greater than 1.3% for placebo; 2.5% for ezetimibe alone; 2.2% for any given statin alone, all doses pooled; and no greater than 2.8% for coadministration, all doses of a given statin pooled. However, this difference was >3% for the following individual treatment groups:

ez + lova 10 mg (-4.4%), ez + prava 10mg (-3.5%), ez + prava 40 mg (-3.9%) and ez + atorva 40 mg (-6.9%): all in which the difference from baseline to endpoint was less compared to the difference from baseline to week 2;

simva 20 mg (+4.2%), atorva 20 mg (+3.5%) and atorva 80 mg (+4.2%): all in which the difference from baseline to endpoint was greater than the difference from baseline to week 2.

Time Course of Therapeutic Response:

As demonstrated in the following figure, the LDL-C lowering effects for all active treatments were seen as early as week 2 and were maintained for the 12 week study duration (note: see the Appendix for the corresponding table and figures for the individual Factorial Coadministration Studies):

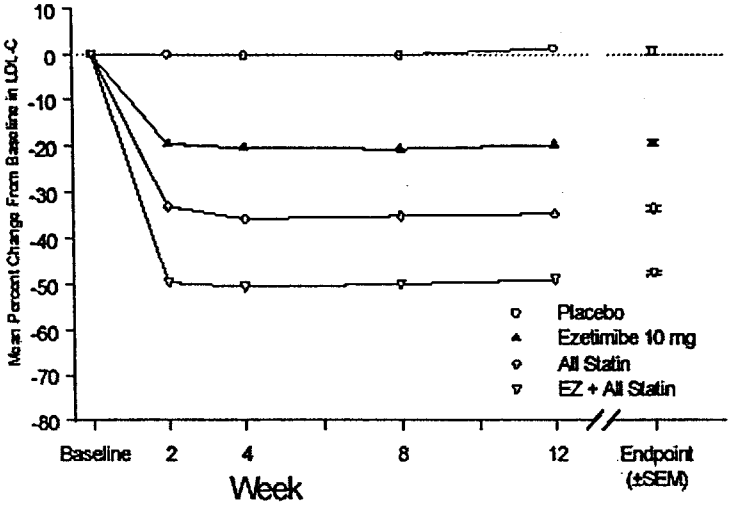

Figure 7 Mean percent change from baseline in plasma concentration of Calculated LDL-C over time and at endpoint for the four treatment groups: Pooled Factorial Coadministration Studies (Intent-to-Treat Data Set)

KEY SECONDARY EFFICACY VARIABLES: TC, TG, HDL-C AND APO B: TC, TG, HDL-C and Apo B: Mean Baseline (mg/dl), TG: Median Baseline: P00474 and P00475 and the Monotherapy Arms (Placebo and Ezetimibe) of the Factorial Coadministration Studies: P00679, P00680, P00691 and P00692:

	P00474		P00475		P00679		P00680		P00691		P00692	
	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez
TC	248.7	249.1	254.5	252.8	266.1	263.8	265.3	272.3	262.5	265.1	261.9	259.1
TG:												
Mean	171.2	163.0	174.8	169.0	168.2	170.4	170.9	190.3	162.6	174.6	156.8	159.1
Median	162.7	158.7	163.7	161.7	162.7	161.0	158.8	182.7	146	165.7	142.8	144.7
HDL-C	51.0	52.1	52.2	52.1	53.7	50.8	52.3	51.0	51.2	50.8	50.4	50.6
Apo B	160.6	161.6	164.4	164.2	166.3	166.1	168.5	174.2	166.7	167.9	168.1	166.5

Mean % Change From Baseline to Endpoint For The Phase III Monotherapy Arms (Placebo and Ezetimibe Treatment Groups) of the Monotherapy and Factorial Coadministration Studies:

Comparison of Least-Square Mean Percent Change from Baseline to Endpoint in Key Secondary Variables Between Ezetimibe Alone and Placebo: Phase III Monotherapy Studies Combined Vs. Factorial Coadministration Studies: Intent-to-Treat Data Set						
	Least-Square Mean % Change From Baseline To Endpoint					
	Phase III Monotherapy Studies[a]			Factorial Coadministration Studies[b]		
	Placebo (n= 430-431)	Ez (n= 1,282-1,288)	Ez - Placebo[c]	Placebo (n= 259)	Ez (n= 259-262)	Ez – Placebo[c]
TC	+0.4	-12.7	-13.1, $p \leq 0.01$	-0.6 to +3.5	-12.7 to -13.5	-12.7 to -17.1, $p \leq 0.01$ for all 4 statins
TG	mean: +3.6, median: 0.0	mean: -4.2, median: -8.0	-7.8, $p \leq 0.01$: P00475 and combined analysis only	mean: +2.0 to +4.4, median: -6.4 to +5.7	mean: -2.1 to -8.3, median: -11.3 to -5.4	-4.1 to -12.0, $p \leq 0.01$: simva only (-12.0%)
HDL-C	-1.6	+1.0	+2.6, $p \leq 0.01$: P00475 and combined analysis, $p \leq 0.05$: P00474	-0.3 to +3.7	+3.5 to +5.1	+0.5 to +4.3, $p \leq 0.05$: lova (+3.8%) and simva (+4.3%) only
Apo B	-1.6	-15.7	-14.1, $p \leq 0.01$	-2.2 to +2.9	-13.6 to -15.4	-12.6 to –18.3, $p \leq 0.01$ for all 4 statins

a= combined analysis: P00474 + P 00475

b= for a given lipid variable, the lowest to the highest mean percent change from baseline to endpoint observed among the individual factorial studies

c= difference between ezetimibe and placebo in mean percent change from baseline

Comments on the above table:

Results were comparable between both studies for TC, TG and Apo-B while HDL-C increases were slightly greater on ezetimibe in the factorial coadministration studies compared to the monotherapy studies. The difference between ezetimibe and placebo was significant for TC, HDL-C and Apo-B in each monotherapy study and for TC and Apo B only in each factorial trial. The difference between ezetimibe and placebo for TG was significant for only 1 of the 2 monotherapy studies (P00475) and 1 of the 4 factorial coadministration studies (Simvastatin only). For this difference in HDL-C in the factorial studies, only Lovastatin and Simvastatin showed significance.

TOTAL CHOLESTEROL (TC):

Mean Baseline Total Cholesterol Levels (mg/dl): Factorial Coadministration Studies:

	Ez	Statin (all doses)	Ez + Statin (all doses)
Lovastatin	263.8	265.1	262.4
Simvastatin	272.3	265.0	263.6
Pravastatin	265.1	262.8	264.0
Atorvastatin	259.1	268.6	267.3

TC: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies:

Mean Percent Change in Plasma Concentration of Total Cholesterol Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)					
	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][a] (95% CI)	[Ez + Statin] – [Statin][b] (95% CI)
Lovastatin	-12.7 (n= 72)	-18.1 (n= 220)	-28.8 (n= 192)	-16.1 (-18.9, -13.3), $p \leq 0.01$	-10.7 (-12.7, -8.7), $p \leq 0.01$
Simvastatin	-13.3 (n= 61)	-25.8 (n= 263)	-36.6 (n= 274)	-23.3 (-26.4, -20.1), $p \leq 0.01$	-10.8 (-12.7, -8.8), $p \leq 0.01$
Pravastatin	-13.2 (n= 64)	-17.2 (n= 205)	-27.1 (n= 204)	-13.9 (-16.5, -11.4), $p \leq 0.01$	-10.0 (-11.7, -8.2), $p \leq 0.01$
Atorvastatin	-13.5 (n= 65)	-32.1 (n= 248)	-41.1 (n= 255)	-27.6 (-30.8, -24.4), $p \leq 0.01$	-9.1 (-11.1, -7.0), $p \leq 0.01$

a= difference between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

b= difference between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Comments on the above table:

The response with respect to TC was similar to that seen with LDL-C. The difference in mean % reduction in TC achieved in the lovastatin, simvastatin, pravastatin and atorvastatin coadministration pools was ~10% compared to the corresponding statin monotherapy pools ($p \leq 0.01$). The difference in mean % reduction between coadministration and ezetimibe alone pooled groups ranged from 14 to 28% and was also statistically significant ($p \leq 0.01$) in each of the 4 factorial studies.

TC: Individual Treatment Groups:

Mean Percent Change in Total Cholesterol Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)

	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[a]	N= 72[a]	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ	0.5	-12.7	-14.5	-24.2	-18.6	-29.5	-21.3	-32.8	-	-
Diff. in mean % Δ (95% CI)		-13.3 (-16.7, -9.8), p≤0.01[b]		-9.6 (-13.1, -6.2), p≤0.01[c]		-10.8 (-14.3, -7.4), p≤0.01[c]		-11.6 (-15.0, -8.1), p≤0.01[c]		
Simvastatin:	N= 70	N= 61	N= 70	N= 67	N= 61	N= 69	N= 65	N= 73	N= 67	N= 65
Mean % Δ	-0.6	-13.3	-18.4	-32.5	-26.1	-32.7	-27.2	-39.7	-31.6	-41.4
Diff. in mean % Δ (95% CI)		-12.7 (-16.6, -8.8), p≤0.01[b]		-14.1 (-17.9, -10.3), p≤0.01[c]		-6.6 (-10.5, -2.7), p≤0.01[c]		-12.5 (-16.2, -8.7), p≤0.01[c]		-9.9 (-13.8, -6.0), p≤0.01[c]
Pravastatin:	N= 65	N= 64	N= 66	N= 71	N= 69	N= 66	N= 70	N= 67	-	-
Mean % Δ	+0.2	-13.2	-14.7	-24.3	-15.0	-27.5	-21.8	-29.6	-	-
Diff. in mean % Δ (95% CI)		-13.4 (-16.6, -10.2), p≤0.01[b]		-9.6 (-12.6, -6.5), p≤0.01[c]		-12.5 (-15.5, -9.4), p≤0.01[c]		-7.9 (-10.9, -4.8), p≤0.01[c]		
Atorvastatin:	N= 60	N= 65	N= 60	N= 65	N= 60	N= 62	N= 66	N= 65	N= 62	N= 63
Mean % Δ	+3.5	-13.5	-25.8	-38.0	-29.9	-39.2	-32.5	-41.7	-40.2	-45.7
Diff. in mean % Δ (95% CI)		-17.1 (-21.2, -12.9), p≤0.01[b]		-12.2 (-16.3, -8.0), p≤0.01[c]		-9.4 (-13.6, -5.2), p≤0.01[c]		-9.2 (-13.3, -5.1), p≤0.01[c]		-5.5 (-9.7, -1.4), p≤0.01[c]

a= sample size at baseline

b= pairwise comparison of ezetimibe versus placebo

c= pairwise comparison of ez + statin to the same dose of statin

Comments on the above table:

The difference between ezetimibe and placebo for the mean % reduction in TC was statistically significant ($p < 0.01$) across all statins studied, with an additional reduction of ~14% in TC with ezetimibe alone compared to placebo. The incremental mean percent change attributable to coadministration of ezetimibe with each dose of statin was significantly different ($p \leq 0.01$) from the corresponding statin dose alone (lovastatin: additional 10 to 12% TC lowering with coadministration compared to same dose of statin alone; simvastatin: additional 7 to 14% TC ↓; pravastatin: additional 8 to 13% ↓ and atorvastatin, additional 6 to 12% decrease in TC).

Pairwise Comparisons Between Coadministration and Statin Alone in Mean % Change from Baseline to Endpoint in TC (ITT):

Difference from the same dose of statin alone: see the above table and, for additional comparisons, see the table below:

Lovastatin:

	Ez + Lova 10mg	Ez + Lova 20mg	Ez + Lova 40mg
Diff, from next higher dose of lova alone in mean % Δ from base (95% CI) (p value)	-5.5 (-9.0, -2.1), p < 0.01	-8.2 (-11.7, -4.7), p < 0.01	Not applicable
Diff. from second higher dose of lova alone in mean % Δ from base(95%CI) (p value)	-2.9 (-6.3, +0.6), not significant: p= 0.10	Not applicable	Not applicable

Simvastatin:

	Ez+Simva 10	Ez+Simva 20	Ez+Simva40	Ez+Simva 80
Diff, from next higher dose of simva alone in mean % Δ from base (95% CI) (p value)	-6.4 (-10.3, -2.5), p<0.01	-5.4 (-9.3, -1.6), p<0.01	-8.1 (-11.9, -4.4), p<0.01	Not applicable
Diff. from second higher dose of simva alone in mean % Δ from base(95%CI) (p value)	-5.3 (-9.1, -1.4), p<0.01	-1.1 (-4.9, +2.7), not significant: p = 0.57	Not applicable	Not applicable
Diff. from highest dose of simva alone in mean % Δ from base(95%CI) (p value)	-0.9, p= 0.64	Not applicable	Not applicable	Not applicable

Pravastatin:

	Ez + Prava 10mg	Ez + Prava 20mg	Ez + Prava 40mg
Diff, from next higher dose of prava alone in mean % Δ from base (95% CI) (p value)	-9.2 (-12.3, -6.2), p < 0.01	-5.7 (-8.8, -2.6), p < 0.01	Not applicable
Diff. from second higher dose of prava alone in mean % Δ from base(95%CI) (p value)	-2.5 (-5.5, +0.54), not significant: p = 0.11	Not applicable	Not applicable

Atorvastatin:

	Ez+Atorva 10	Ez+Atorva 20	Ez+Atorva40	Ez+Atorva 80
Diff, from next higher dose of atorva alone in mean % Δ from base (95% CI) (p value)	-8.1 (-12.3, -4.0), p<0.01	-6.7 (-10.9, -2.6), p<0.01	-1.5 (-5.7, +2.6), not significant: p =0.47	Not applicable
Diff. from second higher dose of atorva alone in mean % Δ from base(95%CI) (p value)	-5.5 (-9.6, -1.4), p<0.01	0.94 (-3.2, +5.1), not significant: p = 0.66	Not applicable	Not applicable
Diff. from highest dose of atorva alone in mean % Δ from base(95%CI) (p value)	+2.2, p= 0.30	Not applicable	Not applicable	Not applicable

Summary Statement for the 4 Pairwise Comparison Tables:

Except for ez + atorva 40 mg vs. atorva 80 mg, for a given statin dose, the incremental mean % change in TC attributable to coadministration was significantly different from the corresponding and next higher dose of statin alone ($p \leq 0.01$). In addition, mean % reductions in TC achieved with the lowest dose of statin tested, 10 mg, coadministered with ezetimibe was similar to (within 3%) those achieved with the highest statin monotherapy dose tested.

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ON ORIGINAL

TRIGLYCERIDES (TG):

Mean and Median Baseline Triglyceride Levels (mg/dl): Factorial Coadministration Studies:

	Ez		Statin (all doses)		Ez + Statin (all doses)	
	Mean	Median	Mean	Median	Mean	Median
Lovastatin	170.4	161	178.4	167.2	172.4	163.8
Simvastatin	190.3	182.7	168.9	157	178.8	168
Pravastatin	174.6	165.7	176.9	180	177.1	173.3
Atorvastatin	159.1	144.7	167.6	154.7	174.6	165.3

TG: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies:

Mean Percent Change in Plasma Concentration of Triglycerides Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)					
	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][b] (95% CI)	[Ez + Statin] – [Statin][c] (95% CI)
Lovastatin:	(n= 72)	(n= 220)	(n= 192)		
Mean:	-2.8	-11.2	-21.7	-18.9 (-25.6, -12.1),	-10.5 (-15.3, -5.7),
Median[a]:	-4.8	-12.1	-25.3	$p < 0.01$	$p < 0.01$
Simvastatin:	(n= 61)	(n= 263)	(n= 274)		
Mean:	-8.3	-16.6	-24.1	-15.7 (-22.2, -9.2),	-7.4 (-11.3, -3.5),
Median[a]:	-11.3	-19.9	-28.7	$p < 0.01$	$p < 0.01$
Pravastatin:	(n= 64)	(n= 205)	(n= 204)		
Mean:	-2.1	-7.6	-17.6	-15.5 (-24.1, -6.8),	-10.0 (-15.9, -4.1),
Median[a]:	-5.4	-14.2	-20.8	$p < 0.01$	$p < 0.01$
Atorvastatin:	(n= 65)	(n= 248)	(n= 255)		
Mean:	-3.4	-21.5	-29.5	-26.0 (-32.7, -19.4),	-8.0 (-12.3, -3.7),
Median[a]:	-5.1	-24.5	-32.8	$p < 0.01$	$p < 0.01$

a= due to the known variability associated with plasma TG levels, median % changes from baseline to endpoint were also examined.

b= difference in mean percent change between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

c= difference in mean percent change between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Comments on the above table:

The difference in mean percent change from baseline in plasma TG concentrations was significant ($p < 0.01$) between the pooled coadministration group and statin monotherapy and between coadministration and ezetimibe alone, the differences ranging from –7 to –11% and -16 to –26%, respectively.

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TG: Individual Treatment Groups:

Mean and Median[a] Percent Change in Triglycerides Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)

	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[b]	N= 72[b]	N= 73[b]	N= 65[b]	N= 74[b]	N= 62[b]	N= 73[b]	N= 65[b]	-	-
Median % Δ	+5.7	-4.8	-10.9	-18.8	-11.9	-27.1	-15.3	-27.3	-	-
Mean % Δ	+4.2	-2.8	-11.6	-17.6	-10.8	-24.5	-11.1	-22.9	-	-
Diff. in mean % Δ (95% CI)		-7.0 (-15.4, +1.4), NS: p= 0.10[c]		-6.0 (-14.3, +2.3), NS: p= 0.16[d]		-13.7 (-22.1, -5.3), p≤0.01[d]		-11.8 (-20.1, -3.5), p≤0.01[d]		
Simvastatin:	N= 70	N= 61	N= 70	N= 67	N= 61	N= 69	N= 65	N= 73	N= 67	N= 65
Median % Δ	+1.8	-11.3	-14.0	-26.1	-17.9	-25.2	-23.9	-31.7	-22.6	-31.3
Mean % Δ	+2.4	-8.3	-10.6	-20.4	-14.8	-20.9	-20.6	-26.7	-20.5	-28.3
Diff. in mean % Δ (95% CI)		-10.7 (-18.7, -2.7), p≤0.01[c]		-9.8 (-17.6, -2.1), p=0.01[d]		-6.1 (-14.1, +2.0), NS: p= 0.14[d]		-6.1 (-13.9, +1.8), NS: p= 0.13[d]		-7.7 (-15.8, +0.3), NS: p= 0.06
Pravastatin:	N= 65	N= 64	N= 66	N= 71	N= 69	N= 66	N= 70	N= 67	-	-
Median % Δ	-0.9	-5.4	-14.2	-22.9	-8.1	-20.6	-19.2	-20.7	-	-
Mean % Δ	+2.0	-2.1	-7.4	-20.0	-2.8	-14.9	-12.5	-17.9	-	-
Diff. in mean % Δ (95% CI)		-4.1 (-14.8, +6.5), NS: p= 0.45[c]		-12.6 (-22.9, -2.3), p=0.02[d]		-12.1 (-22.4, -1.8), p=0.02[d]		-5.4 (-15.6, +4.9), NS: p= 0.03[d]		
Atorvastatin:	N= 60	N= 65	N= 60	N= 65	N= 60	N= 62	N= 66	N= 65	N= 62	N= 63
Median % Δ	-6.4	-5.1	-20.8	-31.1	-22.7	-30.0	-24.4	-33.8	-30.6	-40.0
Mean % Δ	+4.4	-3.4	-16.3	-25.8	-19.3	-27.0	-19.9	-30.0	-30.4	-35.1
Diff. in mean % Δ (95% CI)		-7.9 (-16.4, +0.7), NS: p= 0.07		-9.5 (-18.0, -0.9), p=0.03[d]		-7.7 (-16.3, +1.0), NS: p = 0.08		-10.2 (-18.6, -1.7), p=0.02[d]		-4.7 (-13.3, +3.9), NS: p = 0.28[d]

a= due to the known variability associated with plasma TG levels, median % changes from baseline to endpoint were also examined.

b= sample size at baseline

c= pairwise comparison of ezetimibe versus placebo

d= pairwise comparison of ez + statin to the same dose of statin

Comments on the above table:

The difference between ezetimibe and placebo for the mean % change from baseline TG levels was statistically significant ($p < 0.01$) for simvastatin only, with ezetimibe resulting in an additional 11% reduction in TG. Although greater TG lowering occurred with coadministration

compared to the corresponding statin dose alone, this difference was not always statistically significant.

Pairwise Comparisons in Mean Percent Change from Baseline to Endpoint in TG (ITT): As demonstrated in the above table, the difference between coadministration and the same dose of statin alone, yielded variable results. Some comparisons demonstrated statistical significance and others did not and results varied among the 4 statins studied. Comparisons between coadministration and higher doses of statin alone did not, in general, yield statistically significant differences. The 2 exceptions were: ez + lova 20 mg vs. lova 40 mg where the additional 13% reduction in TG with coadministration was statistically significant ($p < 0.01$). The other exception was ez + prava 10 mg vs. prava 20 mg where the additional 17% reduction in TG with coadministration was statistically significant ($p < 0.01$).

With one exception, coadministration of ezetimibe with the lowest dose of statin tested resulted in the same or greater lowering of TG concentrations as the highest statin monotherapy dose tested. The exception was ez + atorva 10 mg vs. atorva 80 mg with atorva 80 mg alone resulting in an additional ~5% lowering in TG levels compared to coadministration but this difference was not statistically significant ($p= 0.28$).
[sources used were the individual study reports: lovastatin (volume 379, pages 536 and 538, simvastatin (volume 393, pages 572 and 574, pravastatin (volume 407, pages 543 and 545 and atorvastatin, volume 419, pages 558 and 560].

Mean Percent Change in Plasma Concentration of TG Between Baseline and Endpoint: Factorial Coadministration Studies: Intent-to-Treat Data Set			
	Ezetimibe + Statin 10mg	Highest Statin Dose	[Ez + Statin 10 mg] – [Highest Statin Dose Tested]
Lovastatin	-17.6 (n= 65)	-11.1 (n= 73)	-6.5 (-14.8, +1.9), NS: p= 0.13
Simvastatin	-20.4 (n= 67)	-20.5 (n= 67)	+0.1, p= 0.98
Pravastatin	-20.0 (n= 71)	-12.5 (n= 70)	-7.5 (-17.6, +2.7), NS: p= 0.15
Atorvastatin	-25.8 (n= 65)	-30.4 (n= 62)	+4.6, p= 0.28

HDL-C:

Mean Baseline HDL-C Levels (mg/dl): Factorial Coadministration Studies:

	Ez	Statin (all doses)	Ez + Statin (all doses)
Lovastatin	50.8	50.6	50.3
Simvastatin	51.0	51.1	50.4
Pravastatin	50.8	49.8	51.7
Atorvastatin	50.6	53.7	50.8

HDL-C: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies: (note: sample size is that at baseline):

Mean Percent Change in Plasma Concentration of HDL-C Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)					
	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][a] (95% CI)	[Ez + Statin] – [Statin][b] (95% CI)
Lovastatin	+3.5 (n= 72)	+4.0 (n= 220)	+8.6 (n= 192)	+5.1 (2.2, 8.0), p < 0.01	+4.5 (2.5, 6.6), p < 0.01
Simvastatin	+5.1 (n= 61)	+6.9 (n= 263)	+9.3 (n= 274)	+4.1 (0.6, 7.6), p= 0.02	+2.4 (0.3, 4.5), p= 0.03
Pravastatin	+4.1 (n= 64)	+6.7 (n= 205)	+8.1 (n= 204)	+4.0 (0.8, 7.3), p= 0.02	+1.4 (-0.8, +3.7), not significant: p=0.22
Atorvastatin	+4.2 (n= 65)	+4.3 (n= 248)	+7.3 (n= 255)	+3.1 (-0.01, +6.3), p = 0.05	+3.1 (1.1, 5.1), p < 0.01

a= difference between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

b= difference between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Comments on the above table:

Except for pravastatin, pooled coadministration of ezetimibe with statin resulted in statistically significantly ($p \leq 0.05$) greater increases in HDL-C compared to pooled statin (additional 2-5% increase) or to ezetimibe alone (additional 3-5% increase). For pravastatin, only pooled coadministration to ezetimibe alone was statistically significant.

HDL-C: Individual Treatment Groups:

Mean Percent Change in HDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)										
	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[a]	N= 72[a]	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ	-0.3	3.5	+4.7	+7.9	+2.6	+8.7	+4.8	+9.1	-	-
Diff. in mean % Δ (95% CI)		+3.8 (0.2, 7.4), p=0.04[b]		+3.2 (-0.4, +6.8), NS: p=0.08[c]	+2.6	+6.1 (2.5, 9.7), p<0.01[c]		+4.3 (0.8, 7.9), p=0.02[c]		
Simvastatin:	N= 70	N= 61	N= 70	N= 67	N= 61	N= 69	N= 65	N= 73	N= 67	N= 65
Mean % Δ	+0.9	+5.1	+7.6	+8.6	+5.6	+9.2	+6.1	+11.0	+8.2	+8.4
Diff. in mean % Δ (95% CI)		+4.3 (-0.1, +8.6), p=0.05[b]		+1.0 (-3.2, +5.1), NS: p=0.66[c]		+3.6 (-0.7, +7.9), NS: p=0.10[c]		+4.9 (0.7, 9.1), p=0.02[c]		+0.2 (-4.2, +4.5), NS: p=0.93[c]
Pravastatin:	N= 65	N= 64	N= 66	N= 71	N= 69	N= 66	N= 70	N= 67	-	-
Mean % Δ	+2.0	+4.1	+5.6	+8.4	+8.2	+7.8	+6.1	+8.1	-	-
Diff. in mean % Δ (95% CI)		+2.1 (-1.9, +6.2), NS: p=0.31[b]		+2.8 (-1.1, +6.7), NS: p=0.16[c]		-0.5 (-4.4, +3.4), NS: p=0.81[c]		+2.0 (-1.9, +5.9), NS: p=0.32[c]		
Atorvastatin:	N= 60	N= 65	N= 60	N= 65	N= 60	N= 62	N= 66	N= 65	N= 62	N= 63
Mean % Δ	+3.7	+4.2	+6.5	+9.0	+4.0	+9.2	+3.8	+4.6	+2.8	+6.6
Diff. in mean % Δ (95% CI)		+0.5 (-3.6, +4.5), NS: p=0.82[b]		+2.6 (-1.5, +6.6), NS: p=0.22[c]		+5.3 (1.1., 9.4), p=0.01[c]		+0.8 (-3.2, +4.8), NS: p=0.69[c]		+3.7 (-0.3, +7.8), NS: p=0.07[c]

a= sample size at baseline

b= pairwise comparison of ezetimibe versus placebo

c= pairwise comparison of ez + statin to the same dose of statin

Comments on the above table:

The difference between ezetimibe alone and placebo for the mean % reduction in HDL-C from baseline to endpoint was statistically significant ($p \leq 0.05$) for only 2 of the 4 factorial studies: lovastatin and simvastatin. The comparison between coadministration and the corresponding statin dose alone was variably significant for lovastatin, simvastatin and atorvastatin and was not statistically significant for any of these individual treatment group comparisons for pravastatin.

Pairwise Comparisons in Mean Percent Change from Baseline to Endpoint in HDL-C (ITT):

The analyses by each individual dose of statin was significantly different between coadministration and higher doses of statin alone for lovastatin only and was also significant but not uniformly so for atorvastatin. The increase in HDL-C with the lowest dose of statin

coadministration was the same or higher than that achieved with the respective highest statin-alone dose tested:

Mean Percent Change in Plasma Concentration of HDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: Intent-to-Treat Data Set			
	Ezetimibe + Statin 10mg	Highest Statin Dose	[Ez + Statin 10 mg] – [Highest Statin Dose Tested]
Lovastatin	+7.9 (n= 65)	+4.8 (n= 73)	+3.0 (-0.5, +6.6), NS: p= 0.10
Simvastatin	+8.6 (n= 67)	+8.2 (n= 67)	+0.4, p= 0.87
Pravastatin	+8.4 (n= 71)	+6.1 (n= 70)	+2.3 (-1.6, +6.1), NS: p= 0.25
Atorvastatin	+9.0 (n= 65)	+2.8 (n= 63) (note: mean % Δ was 3.8-6.5% at lower doses)	+6.2, p < 0.01

APOLIPOPROTEIN B (Apo B):

Mean Baseline Apo B Levels (mg/dl): Factorial Coadministration Studies:

	Ez	Statin (all doses)	Ez + Statin (all doses)
Lovastatin	166.1	170.1	169.3
Simvastatin	174.2	169.9	168.0
Pravastatin	167.9	169.4	167.5
Atorvastatin	166.5	167.6	170.3

Apo B: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies:

Mean Percent Change in Plasma Concentration of Apo B Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)					
	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][a] (95% CI)	[Ez + Statin] – [Statin][b] (95% CI)
Lovastatin	-13.6 (n= 71)	-21.0 (n= 218)	-33.2 (n= 192)	-19.6 (-22.9, -16.3), p < 0.01	-12.3 (-14.6, -9.2), p < 0.01
Simvastatin	-14.2 (n= 61)	-29.8 (n= 261)	-40.7 (n= 272)	-26.6 (-30.3, -22.8), p < 0.01	-10.9 (-13.2, -8.6), p < 0.01
Pravastatin	-14.8 (n= 64)	-20.0 (n= 201)	-30.2 (n= 201)	-15.4 (-19.3, -11.4), p < 0.01	-10.2 (-12.9, -7.4), p < 0.01
Atorvastatin	-15.4 (n= 63)	-36.1 (n= 247)	-45.4 (n= 255)	-30.0 (-34.0, -26.0), p < 0.01	-9.3 (-11.9, -6.7), p < 0.01

a= difference between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

b= difference between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Comments on the above table:

The differences in mean % change from baseline to endpoint for Apo B between the coadministration pool versus the statin monotherapy and the ezetimibe monotherapy pools were statistically significant (p < 0.01) with an additional 15-30% Apo B reduction with coadministration compared to ezetimibe alone and 9-12% compared to statin alone.

Apo B: Individual Treatment Groups:

Mean Percent Change in Apo B Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)

	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[a]	N= 71[a]	N= 72[a]	N= 65[a]	N= 73[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ	+1.1	-13.6	-16.7	-27.3	-21.0	-34.2	-25.2	-38.3	-	-
Diff. in mean % Δ (95% CI)		-14.7 (-18.8, -10.6), p<0.01		-10.6 (-14.7, -6.5), p<0.01		-13.2 (-17.3, -9.0), p<0.01		-13.1 (-17.1, -9.0), p<0.01		
Simvastatin:	N= 70	N= 61	N= 69	N= 66	N= 60	N= 69	N= 65	N= 72	N= 67	N= 65
Mean % Δ	0.0	-14.2	-21.1	-35.1	-29.0	-36.3	-32.0	-44.9	-37.1	-46.6
Diff. in mean % Δ (95% CI)		-14.2 (-18.8, -9.5), p<0.01		-14.1 (-18.7, -9.5), p<0.01		-7.3 (-12.0, -2.6), p<0.01		-12.9 (-17.5, -8.3), p<0.01		-9.4 (-14.1, -4.7), p<0.01
Pravastatin:	N= 65	N= 64	N= 63	N= 70	N= 69	N= 65	N= 69	N= 66	-	-
Mean % Δ	-2.2	-14.8	-15.6	-26.9	-18.2	-31.3	-26.4	-32.4	-	-
Diff. in mean % Δ (95% CI)		-12.6 (-17.5, -7.8), p<0.01		-11.4 (-16.1, -6.6), p<0.01		-13.1 (-17.9, -8.3), p<0.01		-6.0 (-10.8, -1.3), p<0.01		
Atorvastatin:	N= 60	N= 63	N= 60	N= 65	N= 59	N= 62	N= 66	N= 65	N= 62	N= 63
Mean % Δ	+2.9	-15.4	-28.2	-42.8	-33.9	-43.7	-36.6	-45.2	-45.6	-49.8
Diff. in mean % Δ (95% CI)		-18.3 (-23.4, -13.2), p<0.01		-14.6 (-19.7, -9.5), p<0.01		-9.9 (-15.1, -4.7), p<0.01		-8.6 (-13.6, -3.5), p<0.01		-4.2 (-9.3, +1.0), NS: p=0.11

a= sample size at baseline

b= pairwise comparison of ezetimibe versus placebo

c= pairwise comparison of ez + statin to the same dose of statin

Comments on the above table:

Overall, the effect of coadministration therapy on Apo B was consistent with that seen for TC and LDL-C. The difference between ezetimibe and placebo for the mean % reduction in Apo B was statistically significant ($p < 0.01$) across all statins studied, with an additional reduction of ~15% in Apo B with ezetimibe alone compared to placebo. Individually, all coadministration groups showed a statistically significant difference ($p < 0.01$) when compared to the corresponding statin monotherapy dose, with the exception of atorva 80mg coadministration group ($p= 0.11$).

Pairwise Comparisons in Mean Percent Change from Baseline to Endpoint in Apo B (ITT):
Individually, significant differences ($p \leq 0.05$) were noted between each dose of statin coadministered with ezetimibe and the next higher dose of statin monotherapy with 2 exceptions (simvastatin 20 coadministration group vs. simvastatin 40 monotherapy and atorvastatin 40 coadministration group vs. atorvastatin 80 monotherapy group). In all 4 factorial studies, similar

reductions in Apo B were achieved with ezetimibe coadministered with the lowest statin dose tested compared with the highest corresponding statin monotherapy dose:

Mean Percent Change in Plasma Concentration of Apo B Between Baseline and Endpoint: Factorial Coadministration Studies: Intent-to-Treat Data Set			
	Ezetimibe + Statin 10mg	Highest Statin Dose	[Ez + Statin 10 mg] – [Highest Statin Dose Tested]
Lovastatin	-27.3 (n= 65)	-25.2 (n= 73)	-2.1 (-6.1, +2.0), NS: p= 0.32
Simvastatin	-35.1 (n= 66)	-37.1 (n= 67)	+2.0, p= 0.40
Pravastatin	-26.9 (n= 70)	-26.4 (n= 69)	-0.6 (-5.3, +4.1), NS: p= 0.81
Atorvastatin	-42.8 (n= 65)	-45.6 (n= 62)	+2.8, p= 0.28

OTHER SECONDARY EFFICACY VARIABLES: non-HDL-C, HDL_2-C, HDL_3-C, APO A-1, Lp(a), AND THE RATIOS: direct LDL-C/HDL-C and TC/HDL-C:

Non-HDL-C, HDL_2-C, HDL_3-C, Apo A-1, Lp(a), and the ratios: direct LDL-C/HDL-C and TC/HDL-C: Mean Baseline (mg/dl), Median Baseline for Lp(a): P00474 and P00475 and the Monotherapy Arms (Placebo and Ezetimibe) of the Factorial Coadministration Studies: P00679, P00680, P00691 and P00692:

	P00474		P00475		P00679		P00680		P00691		P00692	
	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez	Plac	Ez
Non-HDL-C	Not measured				212.4	213.1	213.0	221.3	211.2	214.3	211.5	208.5
HDL_2-C	20.1	20.4	19.5	19.6	19.6	17.8	19.3	19.0	18.1	19.1	19.0	18.3
HDL_3-C	30.7	31.9	32.4	32.6	33.7	32.9	33.2	32.9	33.2	33.4	31.4	32.5
Apo A-1	151.1	152.7	152.3	152.3	157.1	153.6	155.9	158.8	157.0	157.2	152.5	154.8
Lp(a):												
Mean	33.6	30.8	27.5	33.5	34.3	34.7	30.1	34.7	32.8	32.0	32.9	27.8
Median	20	21	17	22	20.5	21	20.0	25.0	20	26	19.0	19.0
Direct LDL-C/HDL-C	3.4	3.4	3.4	3.4	3.5	3.7	3.6	3.7	3.6	3.7	3.7	3.7
TC/HDL-C	5.1	5.0	5.1	5.1	5.2	5.5	5.3	5.6	5.3	5.5	5.5	5.4

Mean % Change From Baseline to Endpoint For The Phase III Monotherapy Arms (Placebo and Ezetimibe Treatment Groups) of the Factorial Coadministration Studies:

Comparison of Least-Square Mean Percent Change from Baseline to Endpoint in Other Secondary Variables Between Ezetimibe Alone and Placebo: Phase III Monotherapy Studies Combined Vs. Factorial Coadministration Studies: Intent-to-Treat Data Set

	Least-Square Mean % Change From Baseline To Endpoint					
	Phase III Monotherapy Studies[a]			Factorial Coadministration Studies[b]		
	Placebo (n= 418-431)	Ez (n= 1,266-1,288)	Ez - Placebo[c]	Placebo (n= 247-259)	Ez (n= 250-262)	Ez – Placebo[c]
HDL_2-C	-1.5	+1.4	+2.9, $p \leq 0.05$: P00474 only	+2.7 to +10.4	+7.9 to +13.8	+2.2 to +8.1: not signif for any statin
HDL_3-C	+2.4	+4.4	+2.0, $p \leq 0.01$: P00475 only	-1.6 to +5.4	+0.5 to +3.7	-2.1 to to +2.2: not signif for any statin
Apo A-1	+ 1.2	+2.0	+0.8	-1.1 to +2.6	+1.7 to +2.5	-0.1 to +3.6: not signif for any statin
Lp(a)	+7.5	-3.7	-11.1, $p \leq 0.01$: P00474 and combined analysis, $p \leq 0.05$: P00475	+2.1 to +16.1	+0.8 to +15.0	-9.5 to +4.1: not significant for any statin
LDL/HDL	+2.4	-17.8	-20.2, $p \leq 0.01$	-2.0 to +3.5	-21.1 to – 21.8	-19.7 to –25.1, $p \leq 0.01$ for all 4 statins
TC/HDL	+2.4	-13.1	-15.5, $p \leq 0.01$	-1.2 to +1.3	-15.3 to – 17.4	-14.9 to –17.3, $p \leq 0.01$ for all 4 statins
Non-HDL-C	Not measured			-0.7 to +3.8	-16.4 to -17.7	-16.7 to –21.5, $p < 0.01$ for all 4 statins

a= combined analysis: P00474 + P 00475

b= for a given lipid variable, the lowest to the highest mean percent change from baseline to endpoint observed among the individual factorial studies

c= difference between ezetimibe and placebo in mean percent change from baseline

Comments on the above table:

The difference between ezetimibe and placebo for both cholesterol ratios was consistent between the monotherapy and the factorial studies and was significant ($p \leq 0.01$). For HDL_2-C, HDL_3-C and Apo A-1, the difference between ezetimibe and placebo was not significant for either the combined monotherapy studies or for any of the individual factorial studies. This difference for Lp (a) was significant in the monotherapy studies only and likely reflects the well-recognized variability of this parameter.

Non-HDL-C, HDL_2-C, HDL_3-C, APO A-1, Lp(a), AND THE RATIOS: direct LDL-C/HDL-C and TC/HDL-C: Mean Baseline (mg/dl), Median Baseline for Lp(a): Ezetimibe, Statin and Ezetimibe + Statin Treatment Groups: Factorial Coadministration Studies:

	P00679			P00680			P00691			P00692		
	Ez	Statin	Ez+St	Ez	Statin	Ez+St	Ez	Statin	Ez+St	Ez	Statin	Ez+St
Non-HDL	213.1	214.5	212.1	221.3	213.9	213.3	214.3	213.0	212.3	208.5	214.9	216.5
HDL_2	17.8	17.9	17.1	19.0	18.0	18.2	19.1	18.1	18.7	18.3	20.6	19.3
HDL_3	32.9	33.0	33.2	32.9	33.2	32.4	33.4	31.7	33.6	32.5	33.3	31.9
Apo A-1	153.6	155.0	151.8	158.8	154.9	153.6	157.2	154.8	159.6	154.8	163.0	155.9
Lp(a) Mean	34.7	35.1	35.1	34.7	33.0	30.8	32.0	31.8	31.8	27.8	32.7	29.3
Median	21.0	23.5	23.0	25.0	20.0	17.0	26.0	22.5	18.0	19	22	18
LDL/ HDL	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.6	3.7	3.5	3.8
TC/ HDL	5.5	5.5	5.5	5.6	5.4	5.5	5.5	5.5	5.4	5.4	5.3	5.6

Non-HDL-C:

Mean Percent Change in Plasma Concentration of Non-HDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: Pooled Treatment Groups (Intent-to-Treat Data Set)		
Study	All Statin	Ez + All Statin
Lovastatin (P00679): Mean baseline (mg/dl) Mean % Δ from baseline (SEM) Diff. from statin alone (pool of doses) in mean % Δ from base. (95% CI), p value	(n= 220) 214.5 -23.3 (0.8)	(n= 192) 212.1 -37.6 (0.9) -14.3 (-16.7, -11.8), p≤ 0.01
Simvastatin (P00680): Mean baseline (mg/dl) Mean % Δ from baseline (SEM) Diff. from statin alone (pool of doses) in mean % Δ from base. (95% CI), p value	(n= 263) 213.9 -33.6 (0.8)	(n= 274) 213.3 -47.1 (0.8) -13.5 (-15.8, -11.2), p≤ 0.01
Pravastatin (P00691): Mean baseline (mg/dl) Mean % Δ from baseline (SEM) Diff. from statin alone (pool of doses) in mean % Δ from base. (95% CI), p value	(n= 205) 213.0 -22.7 (0.8)	(n= 204) 212.3 -35.6 (0.8) -12.9 (-15.1, -10.8), p≤ 0.01
Atorvastatin (P00692): Mean baseline (mg/dl) Mean % Δ from baseline (SEM) Diff. from statin alone (pool of doses) in mean % Δ from base. (95% CI), p value	(n= 248) 214.9 -41.1 (0.9)	(n= 255) 216.5 -52.3 (0.9) -11.3 (-13.8, -8.7), p≤ 0.01
Means and standard errors in this table are least-square means and standard errors based on the ANOVA model		

Comments on the above table:

The changes seen in non-HDL were similar to those for LDL-C. The differences between pooled coadministration and the pooled statin monotherapy groups were statistically significant ($p \leq 0.01$) for each of the statins tested. Incidentally, the differences between pooled coadministration and the ezetimibe monotherapy groups were also statistically significant ($p \leq 0.01$) for each of the statins tested as well as and between each statin dose coadministered with ezetimibe and the corresponding monotherapy statin dose.

As the following table demonstrates, the lowest dose of statin coadministered with ezetimibe resulted in a similar or better lowering of non-HDL-C than that seen with the corresponding highest dose of statin monotherapy tested:

Mean Percent Change in Plasma Concentration of Non-HDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: Intent-to-Treat Data Set

	Ezetimibe + Statin 10mg	Highest Statin Dose	[Ez + Statin 10 mg] – [Highest Statin Dose Tested]
Lovastatin	-31.4 (n= 65)	-27.4 (n= 73)	-4.0 (-8.2, +0.2), p= 0.06
Simvastatin	-41.8 (n= 67)	-41.0 (n= 67)	Not performed but difference would not be significant based on comparison of mean % Δ
Pravastatin	-31.7 (n= 71)	-28.1 (n= 70)	-3.6 (-7.3, +0.1), p=0.05
Atorvastatin	-49.3 (n= 65)	-50.6 (n= 62)	Not performed but difference would not be significant based on comparison of mean % Δ

For the HDL-C subfractions and Apo A-1, pooled coadministration vs. pooled statin was statistically significant only for the following statins:
Lovastatin: HDL_2-C, $p < 0.01$ and Apo A-1, $p= 0.04$;
Simvastatin: HDL_3-C, $p= 0.02$; see table below:

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Mean Percent Change in Plasma Concentrations of HDL-C Subfractions and Apo A-1 Between Baseline and Endpoint: Factorial Coadministration Studies: Pooled Treatment Groups (Intent-to-Treat Data Set)						
	HDL_2-C		HDL_3-C		Apo A-1	
	All Statin	Ez + All Statin	All Statin	Ez + All Statin	All Statin	Ez + All Statin
Lovastatin (P00679): Mean baseline (mg/dl) Mean % Δ from base(SEM **Diff. from statin alone in mean % Δ from base. (95% CI), p value**	(n= 212) 17.9 (0.5) 8.3 (2.1)	(n= 187) 17.1 (0.4) 15.7 (2.2) **7.4 (1.6, 13.3), p< 0.01**	(n= 212) 33.0 (0.9) 2.6 (1.0)	(n= 187) 33.2 (0.9) 7.0 (1.1) **4.3 (1.4, 7.3) not signif.**	(n= 218) 155.0 (1.6) 2.8 (0.8)	(n= 192) 151.8 (1.5) 5.2 (0.8) **2.4 (0.1, 4.7) p= 0.04**
Simvastatin (P00680): Mean baseline (mg/dl) Mean % Δ from base(SEM **Diff. from statin alone in mean % Δ from base. (95% CI), p value**	(n= 258) 18.0 (0.5) 15.7 (1.9)	(n= 269) 18.2 (0.5) 15.1 (1.9) **-0.6 (-5.9, 4.7) not signif.**	(n= 258) 33.2 (0.9) 3.8 (1.1)	(n= 269) 32.4 (0.8) 7.5 (1.1) **3.7 (0.5, 6.8) p= 0.02**	(n= 261) 154.9 (1.6) 5.1 (0.8)	(n= 272) 153.6 (1.5) 5.6 (0.8) **0.5 (-1.8, 2.7) not signif**
Pravastatin (P00691): Mean baseline (mg/dl) Mean % Δ from base(SEM **Diff. from statin alone in mean % Δ from base. (95% CI), p value**	(n= 194) 18.1 (0.5) 17.0 (2.6)	(n= 189) 18.7 (0.5) 17.0 (2.6) **0.1 (-7.1, 7.3) not signif.**	(n= 194) 31.7 (0.8) 5.4 (1.6)	(n= 189) 33.6 (0.9) 4.0 (1.6) **-1.5 (-5.8, 2.9) not signif.**	(n= 201) 154.8 (1.6) 3.6 (0.9)	(n= 202) 159.6 (1.6) 3.8 (0.9) **0.2 (-2.2, 2.5) not signif.**
Atorvastatin (P00692): Mean baseline (mg/dl) Mean % Δ from base(SEM **Diff. from statin alone in mean % Δ from base. (95% CI), p value**	(n= 244) 20.6 (0.5) 14.6 (2.3)	(n= 249) 19.3 0.5) 16.7 (2.3) **2.1 (-4.3, 8.5) not signif.**	(n= 244) 33.3 (0.9) 1.4 (1.1)	(n= 249) 31.9 (0.8) 4.4 (1.1) **3.0 (-0.1, 6.1) not signif**	(n= 247) 163.0 (1.6) 0.9 (0.8)	(n= 255) 155.9 (1.6) 2.0 (0.8) **1.1 (-1.0, 3.2) not signif**
Means and standard errors in this table are least-square means and standard errors based on the ANOVA model						

For Lp(a), pooled coadministration vs. pooled statin was not statistically significant ($p > 0.05$) in any of the 4 factorial studies.

For the two cholesterol ratios, the patterns of change were similar and the results were consistent among the 4 studies. The difference in mean percent change in both ratios between the pooled coadministration treatment group and the pooled monotherapy statin treatment group was statistically significant ($p \leq 0.01$) for each statin studied. In addition, the results by individual dose showed a significant difference between the coadministration vs. the corresponding monotherapy treatments ($p \leq 0.01$).

Significant differences ($p \leq 0.01$) in cholesterol ratios were also noted between each dose of statin coadministration and the next higher dose of statin monotherapy. The only exception was atorvastatin 40 mg + ezetimibe which was not statistically different from 80 mg alone for direct LDL/HDL ($p= 0.32$). Coadministration of ezetimibe and the lowest statin dose resulted in a similar or greater mean percent change in both ratios when compared with the highest dose of statin alone.

Exploratory Analysis:
At the time the clinical program for ezetimibe was established, the NCEP ATP II guidelines were still in effect. For those subjects with LDL-C concentrations above target at baseline, a greater proportion ($p \leq 0.01$) of subjects in the pooled coadministration treatment group achieved their target LDL-C at endpoint as compared to those in the pooled statin monotherapy treatment group:

Number (%) of Subjects With Primary Hypercholesterolemia Who Achieved Target Plasma Concentration of LDL-C At Endpoint By Baseline LDL-C and CV Risk Factors: Factorial Coadministration Studies (ITT Data Set)		
	All Statin: below goal only at endpoint, not baseline	Ez + All Statin below goal only at endpoint, not baseline
Lovastatin	121/218 (63%)	136/190 (84%)
Simvastatin	191/261 (83%)	214/268 (93%)
Pravastatin	104/203 (59%)	148/204 (83%)
Atorvastatin	188/245 (87%)	216/252 (95%)

CO-ADMINISTRATION WITH STATINS INDICATION:
EZETIMIBE ADDED TO ON-GOING STATIN THERAPY: ADD-ON STUDY: P02173:

Primary Efficacy Variable: Mean Percent Change in LDL:-C From Baseline To Endpoint:

Percent Change in Plasma Concentration of LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set		
LDL-C	Statin + Placebo	Statin + Ezetimibe
Mean baseline (mg/dl)	138.8 (n= 390)	138.1 (n= 379)
Mean Endpoint (mg/dl) LS mean percent change from baseline[a]	132.8 (n= 388) -3.7	102.5 (n= 375) -25.1
Difference from placebo in LS mean % change from baseline (95% CI)[a]	-21.5 (-23.5, -19.5) $p < 0.001$	
a: Least-square means based on the ANOVA model		

Comment on the above table:
Addition of ezetimibe 10 mg/day to ongoing statin monotherapy further reduced calculated LDL-C by 21.5% with respect to mean percent change from baseline compared with statin alone ($p < 0.001$). This additional decrease was observed as early as week 2 and was maintained to endpoint as demonstrated in the following figure:

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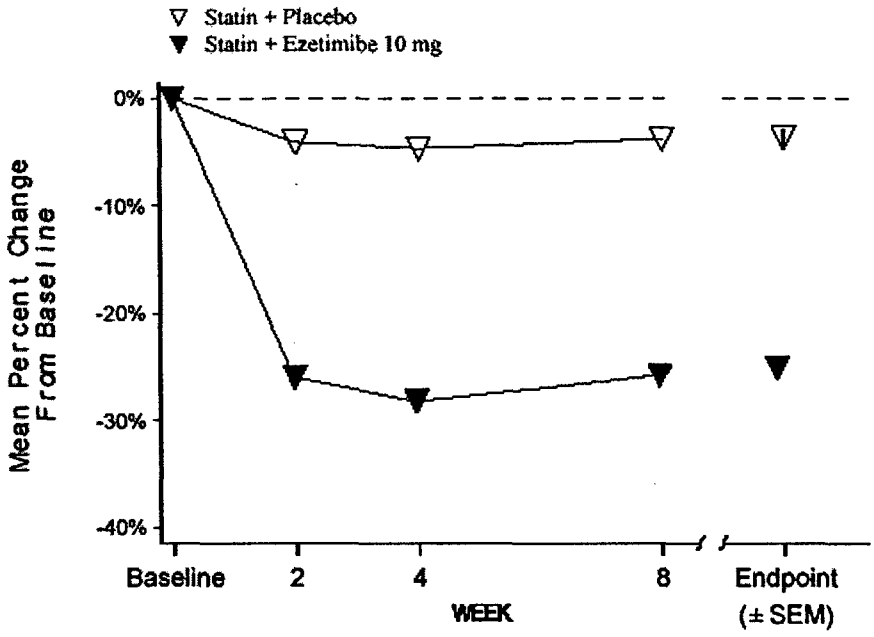

Figure 1 LS Mean Percent Change From Baseline in Plasma Concentration of LDL-C Over Time and at Endpoint in the two Treatment Groups: Intent-to-Treat Data Set

Source Data: Section 14.2.2.1.1.1, n = 367 to 390 at each time point for statin + placebo, and 360 to 379 at each time point for statin + ezetimibe 10 mg (SEM = standard error of the LS mean).

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Results by individual statin are presented in the following table;

Mean Percent Change in Plasma Concentration of LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set: By Individual Statin		
LDL-C	Simvastatin + Placebo	Simvastatin + Ezetimibe
Mean baseline (mg/dl)	137.6 (n= 117)	141.4 (n= 123)
Mean endpoint (mg/dl) LS mean percent change from baseline[a]	133.2 -3.1	102.6 -26.8
Diff. from placebo in LS mean % change from baseline (95% CI)	-23.7 (-27.3, -20.1)	
	Atorvastatin + Placebo	Atorvastatin + Ezetimibe
Mean baseline (mg/dl)	140.2 (n= 162)	141.2 (n= 146)
Mean endpoint (mg/dl) LS mean percent change from baseline[a]	133.8 -4.0	104.8 -25.0
Diff. from placebo in LS mean % change from baseline (95% CI)	-21.0 (-24.2, -17.8)	
	Other[b] + Placebo	Other[b] + Ezetimibe
Mean baseline (mg/dl)	138.2 (n= 111)	130.4 (n= 110)
Mean endpoint (mg/dl) LS mean percent change from baseline[a]	131.1 -3.8	99.1 -23.5
Diff. from placebo in LS mean % change from baseline (95% CI)	-19.7 (-23.5, -16.0)	
a: Least-square means based on the ANOVA model; b: other= prevastatin, fluvastatin, lovastatin and cerivastatin		

Comment on the above table:

The addition of ezetimibe to ongoing simvastatin, atorvastatin and other statin therapy further reduced mean changes in LDL-C by –23.7%, -21.0% and –19.7%, respectively compared to simvastatin, atorvastatin and other statin therapy alone.

Secondary Efficacy Variables:

Percentage of Subjects Reaching NCEP ATP II Target LDL-C Levels At Endpoint:

Number (%) of Subjects Who Achieved NCEP II Target Goal For LDL-C At Endpoint: ITT:		
	Statin + Placebo (n= 390)[a]	Statin + Ezetimibe (n= 379)[a]
	(n= 388)[b]	(n= 375)[b]
Below goal at baseline	66 (17.0)	70 (18.7)
Below goal at endpoint	106 (27.3)	283 (75.5)
Below goal at endpoint only	61 (15.7)	218 (58.1)
Below goal at baseline only	21 (5.4)	5 (1.3)
a= number of randomized subjects, b= number of subjects who had baseline and at least one postbaseline value		

Number (%) of Subjects Who Achieved NCEP II Target Goal For LDL-C At Endpoint: ITT Based Upon Subjects Who Were Above LDL-C NCEP ATP II Target Levels At Baseline		
	Statin + Placebo (n= 323)[a]	Statin + Ezetimibe (n= 309)[a]
	(n= 322)[b]	(n= 305)[b]
Below goal at baseline	0	0
Below goal at endpoint	61 (18.9)	218 (71.5)
Below goal at endpoint only	61 (18.9)	218 (71.5)
Below goal at baseline only	0	0
a= number of randomized subjects, b= number of subjects who had baseline and at least one postbaseline value		

Comments on the above tables:

For the entire study cohort, 27.3% of the statin + placebo subjects achieved NCEP ATP II target LDL-C levels at endpoint, whereas 75.5% of the statin + ezetimibe subjects achieved their target goals ($p \leq 0.01$ for the difference between the two treatment groups). For the subjects who were above target levels at baseline, the percentage of subjects who achieved the target LDL-C goal at endpoint were 18.9% and 71.5% for the statin + placebo and statin + ezetimibe groups, respectively.

Key Secondary Efficacy Variables: TC, TG and HDL-C:

Summary Statement of Results:

As the tables below demonstrate, the addition of ezetimibe 10 mg/day to ongoing statin therapy further reduced TC and TG by 14.7% and 11.1%, respectively ($p < 0.001$ for each difference) and increased HDL-C by 1.7% ($p < 0.05$) relative to statin alone. These additional changes were observed as early as week 2 and were maintained throughout the 8-week active treatment phase.

Total Cholesterol:

Mean Percent Change in Plasma Concentration of Total Cholesterol Between Baseline and Endpoint: Intent-to-Treat Data Set		
Total Cholesterol	Statin + Placebo	Statin + Ezetimibe
Mean baseline (mg/dl)	218.9 (n= 390)	217.6 (n= 379)
Mean Endpoint (mg/dl) LS mean percent change from baseline[a]	212.7 (n= 388) -2.3	179.1 (n= 375) -17.1
Difference from placebo in LS mean % change from baseline (95% CI)[a]	-14.7 (-16.2, -13.3) p <0.001	
a: Least-square means based on the ANOVA model		

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Triglycerides:

Median[a] Percent Change in Plasma Concentration of Triglycerides Between Baseline and Endpoint: Intent-to-Treat Data Set		
Triglycerides	Statin + Placebo	Statin + Ezetimibe
Median baseline (mg/dl)	137.0 (n= 390)	136.0 (n= 379)
Median Endpoint (mg/dl) Median percent change from baseline[b]	132.5 (n= 388) -2.9	121.0 (n= 375) -14.0
Difference from placebo in median % change from baseline	-11.1 (p <0.001)	
a: the percent change data of TG had a distribution skewed to the right, and the parametric approach was corroborated with a nonparametric method based upon Turkey's normalized ranks; the interpretation of the results was based upon the nonparametric results. b: Least-square means based on the ANOVA model		

HDL-C:

Mean Percent Change in Plasma Concentration of HDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set		
Total Cholesterol	Statin + Placebo	Statin + Ezetimibe
Mean baseline (mg/dl)	50.2 (n= 390)	49.1 (n= 379)
Mean Endpoint (mg/dl) LS mean percent change from baseline[a]	50.4 (n= 388) +1.0	50.3 (n= 375) +2.7
Difference from placebo in LS mean % change from baseline (95% CI)[a]	+1.7 (0.3, 3.1) p <0.05	
a: Least-square means based on the ANOVA model		

(Note: the ANOVA model for evaluation of the treatment-by-center consisted of the following terms: treatment, center and treatment-by-center interaction. The interaction term was significant for LDL-C and TC ($p < 0.05$). Further examination of these significant interactions indicated that they were attributable to variable results and small sample sizes at some of the centers. The evaluation of the nature of the interaction also showed that the interaction effect was quantitative, not qualitative, in nature).

Other Secondary Efficacy Variables: non-HDL-C, Apo B, Apo A-1, Apo A-II, LDL-C/HDL-C, TC/HDL-C and CRP (C-reactive protein):

Summary Statement of Results:

As the tables below demonstrate, a significant treatment difference ($p < 0.05$) was observed between statin plus ezetimibe versus statin plus placebo for all variables except for Apo A-I ($p > 0.20$).

Intent-to-Treat Data Set (ITT)	Non-HDL-C		Apo B		Apo A-1	
	All Statin	Ez +All Statin	All Statin	Ez +All Statin	All Statin	Ez +All Statin
Mean base[a]	168.6 (n=390)	168.5 (n=379)	141.0(n= 386)	140.7 (n=375)	159.0 (n=386)	157.2 (n=375)
Mean % Δ from base to endpoint	-3.1	-22.8	-3.5	-19.1	-1.3	-1.2
Diff. from placebo in mean % Δ from base[b]	-19.8 (-21.6, -17.9), p < 0.001		-15.6 (-17.6, -13.6), p < 0.001		+0.1 (-1.6, +1.9), p > 0.20	
a= mg/dl b= Least-square means based on the ANOVA model						

Intent-to-Treat Data Set (ITT)	Apo A-II		LDL-C/HDL-C		TC/HDL-C	
	All Statin	Ez +All Statin	All Statin	Ez +All Statin	All Statin	Ez +All Statin
Mean base[a]	33.4 (n=386)	33.3 (n= 375)	2.9 (n= 390)	3.0 (n= 379)	4.6 (n= 390)	4.6 (n= 379)
Mean % Δ from base to endpoint	-0.7	-2.5	-4.1	-26.7	-2.8	-18.7
Diff. from placebo in mean % Δ from base[b]	-1.8 (-3.4, -0.3), p < 0.05		-22.5 (-24.7, -20.4), p < 0.001		-15.9 (-17.6, -14.3), p < 0.001	
a= mg/dl b= Least-square means based on the ANOVA model						

Intent-to-Treat Data Set (ITT)	CRP	
	All Statin	Ez +All Statin
Median base (mg/L)	2.1 (n= 388)	1.7 (n= 376)
Median % Δ from base to endpoint	0.0	-9.7
Difference from placebo in median % Δ from baseline[a]	-9.7, p= 0.035	
a= based on nonparametric ANOVA using Turkey's normalized ranks		

Exploratory Analysis:

For the entire study cohort, 26.5% of the statin + placebo subjects achieved NCEP ATP III target LDL-C levels at endpoint, whereas 74.9% of the statin + ezetimibe subjects achieved their target goals ($p \leq 0.01$ for the difference between the two treatment groups). For the subjects who were above target levels at baseline, the percentage of subjects who achieved the target LDL-C goal at endpoint were 18.5% and 71.0% for the statin + placebo and statin + ezetimibe groups, respectively.

Comparison of LDL-C Reduction in the Factorial Studies to the Add-On Study:

Coadministration of ezetimibe and statins in the 4 Factorial Studies produced generally consistent results, with incremental mean percent reductions attributable to ezetimibe ranging from –12.1 to –15.0% for calculated LDL-C. In the Add-On Study, the mean percent change in calculated LDL-C levels achieved with the addition of ezetimibe to ongoing statin therapy relative to placebo was –21.5%. The difference in magnitude of the observed mean percent reductions in plasma LDL-C in the Factorial and Add-On Studies appear to be due to differences in baseline LDL-C values used for calculating percent reductions.

In the Factorial Coadministration Studies, the observed incremental reduction in LDL-C reflects the proportion of the total reduction specifically attributable to the ezetimibe component (i.e. over and above the statin monotherapy effects at corresponding doses). This was calculated by subtracting the % LDL-C reduction in the statin monotherapy pooled group from that obtained in the corresponding statin plus ezetimibe pooled group. Thus, the incremental reduction attributable to ezetimibe was computed relative to plasma LDL-C concentrations obtained prior to administration of any lipid-lowering therapy.

Baseline LDL-C concentrations in the Add-On Study, however, reflect levels achieved while these subjects were already taking statins at constant doses for at least 6 weeks, but had not attained goal. Therefore, in this study, baseline LDL-C levels were not those obtained prior to starting statin therapy. The objective of this trial was to assess the incremental effects of ezetimibe in subjects already receiving a statin but requiring further LDL-C lowering. Therefore, unlike the Factorial Coadministration Studies, in the Add-On Study the observed mean percent changes in LDL-C levels represent values calculated relative to baseline levels that are lower because they already reflect statin-induced LDL-C lowering. It should also be pointed out that the Add-On Study population had a substantially higher incidence of established CHD at baseline and was generally a higher CHD risk cohort compared with the populations recruited for the Factorial Coadministration Studies. There was also a higher proportion of males in the Add-On Study.

In summary, the mean percent reductions in LDL-C in the Factorial Studies were calculated relative to a pre-statin baseline value while in the Add-On Study, the mean percent reduction was calculated relative to an on-statin baseline. When the sponsor took into account the difference in baseline LDL-C concentrations, the incremental percent reduction in LDL-C produced by ezetimibe was consistent across these studies. This point is illustrated in the following table, which shows the mean percent change in LDL-C concentrations in each of the Factorial Coadministration Studies either as the primary endpoint (i.e. relative to the actual baseline value, calculated as the mean percent change) or calculated relative to the statin-alone endpoint values (which corresponds to that used in the Add-On Study). The observed differences for the % change in mean LDL-C concentrations at endpoint between each factorial statin-alone group versus the statin + ezetimibe group ranged from –18.4 to –24.3%, consistent with the observed difference of –22.8% calculated in the same manner for the Add-On Study.

Calculated LDL-C concentrations[a] (mg/dl) at Endpoint in the Pooled Coadministration and Pooled-Statin Alone Arms of the Factorial Coadministration Studies and the Add-On Study and Percent Reductions Calculated Using Mean LDL-C Achieved on Statin Alone Versus Actual Study Baseline Values (Primary Endpoint)

Study	Calculated LDL-C Concentration		% LDL-C Reduction	
	Statin alone (mg/dl)	Statin + Ez (mg/dl)	Study Primary Endpoint	% Difference[b] Using Statin-Alone Baseline
Lovastatin Factorial	133.1	105.6	15.0	20.7
Simvastatin Factorial	114.0	86.3	14.8	24.3
Pravastatin Factorial	132.8	108.3	13.4	18.4
Atorvastatin Factorial	101.1	79.1	12.1	21.8
Add-On Study	132.8	102.5	21.5	22.8

a: calculated LDL-C levels are used in this table because only calculated LDL-C levels were available in the Add-On Study;

b: % Difference= $\frac{\text{(Statin + Ez – Statin alone) x 100}}{\text{Statin-Alone}}$

Conclusion:

In the Factorial Studies, the LDL-C lowering effect of coadministration can be compared, post-hoc, to an "on-statin baseline" by computing the % difference between the mean LDL-C level at endpoint achieved with statin alone to that achieved with coadministration. For the lovastatin, simvastatin, pravastatin and atorvastatin factorial studies, these % differences were 20.7%, 24.3%, 18.4% and 21.8%, respectively. In the Add-On Study, this difference was 22.8% thus demonstrating comparability of LDL-C lowering effect to the Factorial Studies.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH) INDICATION:

Study P01030: A Phase III Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia (HoFH):

[Note: The efficacy analyses are not the raw means but are based on the least squares means from an ANOVA model that extracts effects due to treatment group (statin alone combined group, statin plus Ezetimibe 10 mg combined group) and statin (atorvastatin, simvastatin). Therefore, for a given treatment group, e.g. statin 80mg, the mean baseline, endpoint and the mean % change from baseline may vary among comparisons involving that treament group].

LDL-C:

Mean Percent Change in Plasma Levels of LDL-c Between Baseline and Endpoint: ITT:

	Direct LDL-C		Calculated LDL-C	
	Statin 80 mg N= 17	Eze + Statin 40/80 mg N= 33	Statin 80 mg N= 17	Eze + Statin 40/80 mg N= 33
Baseline (mg/dl)	338.8	313.2	341.0	315.7
Endpoint:				
Mean (mg/dl)	318.5	247.2	321.1	247.7
Mean % Δ from baseline (SEM)	-6.7 (4.2)	-20.7 (3.2)	-6.6 (4.2)	-21.4 (3.2)
Diff. from statin in mean % Δ from base (95% CI)		-14.1 (-24.1, -4.0), p = 0.007		-14.8 (-24.9, -4.7), p= 0.007

Note: all means and standard errors are least-square means and standard errors based on the two-way ANOVA model extracting treatment and statin effects.

Comment on the above table:

Results were similar for direct and calculated LDL-C. Coadministration of ezetimibe plus statin 40/80 mg was significantly more efficacious (~14% additional decrease, $p < 0.01$) than statin 80 mg alone in reducing plasma concentrations of LDL-C from baseline to endpoint.

The LDL-C lowering effects of the ezetimibe coadministration were seen as early as Week 2 and were maintained for the duration of the study:

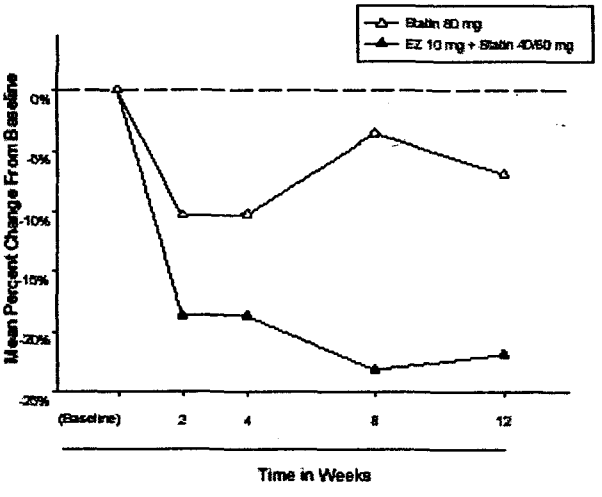

Figure 2 Percent change from baseline in plasma concentration of direct LDL-C over time in the two primary comparison groups, EZ 10 mg + Statin 40/80 mg and Statin 80 mg.

High-Dose Comparison Groups:

Comparison of the high dose treatment groups: Statin 80 mg (pooled Atorva 80 mg and Simva 80 mg) vs. Eze + Statin 80 mg (pooled Ez + Atorva 80 mg and Ez + Simva 80 mg):

Mean % Change in Plasma Concentration of LDL-C Between Baseline and Endpoint: High-Dose Comparison Groups				
	Direct LDL-C		Calculated LDL-C	
	Statin 80 mg (n= 17)	Ez + Statin 80 mg (n= 17)	Statin 80 mg (n= 17)	Ez + Statin 80 mg (n= 17)
Baseline (mg/dl)	341.7	273.3	343.8	275.7
Endpoint: Mean (mg/dl) Mean % Δ from baseline (SEM) Diff. from statin in mean % Δ from base (95% CI)	 319.3 -7.0 (3.5)	 195.8 -27.5 (3.5) -20.5 (-30.0, -11.0), p= 0.0001	 321.9 -7.0 (3.6)	 198.5 -27.5 (3.6) -20.5 (-30.5, -10.6), p= 0.0001

Note: all means and standard errors are least-square means and standard errors based on the two-way ANOVA model extracting treatment and statin effects.

Comment on the above table:

When the high dose treatment groups were compared, the incremental change attributable to ezetimibe was -20.5%, p= 0.001, for both direct and calculated LDL-C concentrations.

Since a statistically significant difference (p= 0.02: 273.3 vs. 341.7 mg/dl) was noted in baseline least-square means for LDL-C between the statin 80 mg and ez + statin 80 mg treatment groups, an analysis of covariance was performed incorporating the baseline LDL-C values as covariates. The sponsor stated that the conclusion remained the same.

Change in LDL-C From Baseline by Treatment Group:

As the following tables demonstrate, a greater reduction in plasma LDL-C levels was observed with ezetimibe coadministered with the statin 80 mg than was observed with ezetimibe coadministered with statin 40 mg:

Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set						
	Atorva 80 mg N= 12	Eze + Atorva 40 N= 12	Eze + Atorva 80 N= 12	Simva 80 N= 5	Eze + Simva 40 N= 4	Eze + Simva 80 N= 5
Mean % Δ from base (SEM)	-3.50 (3.54)	-13.01 (6.35)	-24.66 (3.54)	-10.99 (6.35)	-12.03 (3.54)	-29.82 (6.35)

Change in Plasma Concentration of Calculated LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set						
	Atorva 80 mg N= 12	Eze + Atorva 40 N= 12	Eze + Atorva 80 N= 12	Simva 80 N= 5	Eze + Simva 40 N= 4	Eze + Simva 80 N= 5
Mean % Δ from base (SEM)	-2.22 (3.58)	-13.66 (6.21)	-24.58 (3.58)	-13.01 (6.21)	-14.48 (3.58)	-29.08 (6.21)

Also observe in the above table that the LDL-C reduction achieved with Simva 80 mg was numerically higher than that achieved with Atorva 80 mg.

Primary Efficacy Results for the Subset of Patients With Confirmed Mutations in the LDL Receptor Gene:

Treatment Differences in Mean % Changes in Plasma Concentrations of Direct LDL-C (95% CI) for the Subset of Patients With Genetically Confirmed HoFH	
Geneotype	Differences in Mean Percent Change: Ez + Statin 40/80 mg – Statin 80 mg
True Homozygotes & Compound Heterozygotes (n=32)[a]	-14.4% (-25.1, -3.8)
True Homozygotes (n= 19)	-15.4% (-31.8, 0.9)
Compound Heterozygotes (n= 13)	-13.1% (-25.4, -0.7)
a= excludes 2 subjects with a hx. of genetic diagnosis	

Comment on above table:

Mean incremental changes attributable to ezetimibe for all genetically confirmed HoFH subjects (n= 32) and for true homozygotes (n= 19) and compound heterozygotes (n= 13) ranged from -13.1 to -15.4% and were similar to results obtained for the entire study population.

Secondary Efficacy Analysis: Key Secondary Variables: TC, TG, Apo B and HDL-C:

Mean Baseline Values and Mean Percent Change From Baseline to Endpoint: Intent-to-Treat Data Set				
	Primary Comparison		High-Dose Comparison	
	Statin 80 mg (n= 17)	Ez + Statin 40/80 mg (n= 33)	Statin 80 mg (n= 17)	Ez + Statin 80 mg (n= 17)
Total Cholesterol:				
Mean Baseline (mg/dl)	404.3	379.4	406.9	340.8
Mean % change from baseline to endpoint[a]	-5.3	-18.7	-5.6	-23.7
Diff. from statin 80 mg in mean % Δ from base (95% CI)		-13.3 (-22.1, -4.5), p<0.01		-18.1 (-26.4, -9.8), p<0.01
Triglycerides:				
Mean Baseline (mg/dl)	102.2	109.6	104.9	119.7
Mean % change from baseline to endpoint[a]	-5.8	-10.8	-6.0	-16.8
Median % change from baseline to endpoint[b]	-5.1	-16.7	-5.1	-19.4
Diff. from statin 80 mg in mean % Δ from base (95% CI)		-5.0 (-21.5, 11.5), p= 0.54		-10.7 (-24.4, 2.9), p= 0.12
Apo B:				
Mean Baseline (mg/dl)	269.3	252.9	270.4	228.9
Mean % change from baseline to endpoint[a]	-1.9	-3.7	-0.6	-0.9
Median % change from baseline to endpoint[b]	-4.1	-16.0	-4.1	-17.9
Diff. from statin 80 mg in mean % Δ from base (95% CI)		-1.8 (-22.9, 19.3), p= 0.87		-0.35 (-30.0, 29.3), p= 0.98
HDL-C:				
Mean Baseline (mg/dl)	42.9	41.8	42.1	41.2
Mean % change from baseline to endpoint[a]	4.4	-2.8	4.1	-2.4
Diff. from statin 80 mg in mean % Δ from base (95% CI)		-7.2 (-15.5, 1.1), p= 0.09		-6.5 (-16.9, 3.9), p= 0.21
a= mean values are least-square means based on the two-way ANOVA model extracting treatment and statin effects; b= median percent changes are shown for TG and Apo B due to large interindividual variations in these variables				

Comments on the above table:

Of the key secondary efficacy variables, only mean percent changes in TC were significantly different for the primary comparison and high-dose groups. Note that ezetimibe exerted a lowering effect on HDL-C in this patient population. Not shown here, but to be noted were the mean changes in Apo B across treatment groups which ranged from –18.7 to +33.2%. The Ez + Simva 80 mg treatment group had a mean change in Apo B of +33.2%, which was discordant with the -34.5% change observed for direct LDL-C. This positive rather than negative change in Apo B concentrations was largely attributable to one subject with a change of +209.1%. The impact of this outlier on the mean values is reflected in the difference between the mean and median values for percent change in Apo B.

Other Secondary Efficacy Variables: HDL_2-C, HDL_3-C, Apo A-1, Lp(a) and the ratios LDL-C/HDL-C and TC/HDL-C:

Least-Square Mean Percent Changes (SEM) from Baseline to Endpoint in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set:

Variables	Statin 80 mg (n = 17)	EZ 10 mg + Statin 40/80 mg (n = 33)	[EZ + Statin 40/80] – [Statin 80]: p-value
HDL2-C	7.82 (11.8)	8.62 (9.84)	p = .96
HDL3-C	2.22 (4.33)	-2.77 (3.62)	p = .35
Apo A-1	0.93 (2.93)	-0.75 (2.26)	p = .63
Direct LDL-C:HDL-C	-10.09 (5.56)	-17.00 (4.17)	p = .30
TC:HDL-C	-8.79 (4.81)	-15.19 (3.61)	p = .27
Lp(a)	21.62 (14.4)	6.96 (10.9)	p = .40

SEM = standard error of the least-square mean.

Note: not every patient had an end-of-treatment measurement for every variable. "N" sizes varied from 29 to 33 for the Ezetimibe 10 mg + Statin 40/80 mg group and from 16 to 17 for the Statin 80 mg group.

Comment on above table:

There were no significant differences between ez + statin 40/80 mg and statin 80 mg, the primary efficacy comparison, in the mean percent changes from baseline in the plasma concentrations of the other secondary efficacy variables.

HOMOZYGOUS SITOSTEROLEMIA INDICATION (STUDY P02243 and P02257):

Primary Efficacy Analysis:

Plasma Sitosterol:

Percent Change in Sitosterol (mg/dl) Between Baseline and Endpoint: Modified Intent-to-Treat Population		
Sitosterol (mg/dl)	Placebo (n= 7)	Ezetimibe 10 mg (n= 29)
Baseline	18.5	21.0
Endpoint: Raw mean Raw mean % Δ from baseline (SE) Mean % change from baseline (SE) Diff. from placebo in mean % Δ from baseline (95% CI)	 17.8 4.0 	 16.2 -22.6 (2.2), p < 0.001 -21.0 (2.8) -25.0 (-36.7, -13.2), p < 0.001

Comment on the above table:

The above table demonstrates that plasma sitosterol decreased significantly from baseline and was significantly different from placebo.

The above analysis was performed in the modified intent-to-treat population. As prespecified in the data analysis plan filed prior to unblinding, subjects receiving apheresis were to be excluded from the efficacy analysis. This entailed 1 subject who was randomized to ezetimibe. The subject's baseline sitosterol concentration was – mg/dl; the sitosterol concentrations on weeks 2, 4, 6, and 8 were [redacted] mg/dl, respectively. The mean percent change in plasma sitosterol level from baseline to endpoint (average of weeks 6 and 8 values) was -8.3% in this patient.

As demonstrated in the following table, the effect of ezetimibe on plasma sitosterol concentrations did not differ by concomitant use of bile-acid binding resins. Mean changes (SEM) were –20.4 ± 4.2% for subjects treated with resins versus –23.5 ± 2.6% for subjects not treated with resins:

Mean Percent Changes in Plasma Sitosterol Concentrations According to Stratum of Usage or Non-Usage of Bile Acid Binding Resins: Modified Intent-to-Treat Population		
Sitosterol concentrations (mg/dl)	Ezetimibe: subjects on resins (n= 8)	Ezetimibe: not on resins (n= 21)
Baseline mean	19.1	21.8
Endpoint: Raw mean Mean % Δ from baseline (SEM) 95% CI for mean % change[a]	 14.9 -20.4 (4.2), $p \leq 0.01$ (-29.0, -11.7)	 16.7 -23.5 (2.6), $p \leq 0.01$ (-28.8, -18.2)
a= values are Least-Squares (LS) means and LS standard error (SEM) based on the ANOVA model		

A similar observation was made in subjects taking or not taking statins:
Mean % change from baseline in plasma sitosterol:
Ezetimibe: subjects on statins (n= 7): -23.7%;
Ezetimibe: subjects not on statins (n= 22): -22.3%

The reduction in plasma sitosterol concentration for subjects on ezetimibe during the double-blind treatment period was progressive beginning at week 2, with numerically greater reduction from baseline observed at each subsequent visit:

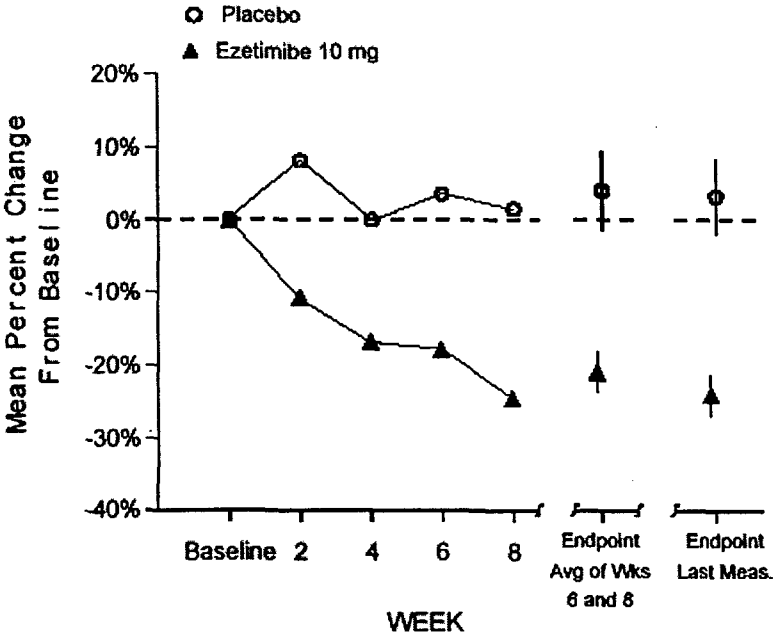

Figure 2 Mean percent change from baseline in plasma concentration of sitosterol over time and at endpoint in the 2 treatment groups: Modified Intent-to-Treat Population
Source Data: **Section 14.2.2.3.1.**

Secondary Efficacy Analysis:

Efficacy Variable	Placebo (n= 7)	Ezetimibe (n= 29)
Campesterol:		
Raw mean value (mg/dl)	9.7	11.0
Mean % Δ from baseline (SE)	3.2 (5.5)	-24.3 (2.9)
95% CI for mean percent change[a]	(-7.9, 14.3)	(-30.2, -18.4)
Diff. from placebo in mean % Δ from base.(95% CI	-27.5 (-39.6, -15.4), p < 0.001	
LDL-c:		
Median value (mg/dl)	89.1	95.3
Median[b] % Δ from baseline (SE)	16.7 (19.7)	-13.6 (4.0)
95% CI for **median** percent change[a]	(-31.6, 64.9)	(-21.7, -5.5)
Diff. from placebo in **median** % Δ from baseline[c]	-30.3, p= 0.108= not significant[d]	
LDL Sterols[e]*:*		
Raw mean value (mg/dl)	119.9	130.9
Mean % Δ from baseline (SE)	18.4 (7.7)	-14.9 (4.1)[f]
95% CI for mean percent change[a]	(2.8, 34.0)	(-23.2, -6.6)
Diff. from placebo in mean % Δ from base.(95% CI	-33.3 (-50.4, -16.2), p < 0.001	

HDL-C:		
Raw mean value (mg/dl)	33.3	39.8
Mean % Δ from baseline (SE)	8.3 (6.1)	6.2 (3.2)
95% CI for mean percent change[a]		
Diff. from placebo in mean % Δ from base.(95% CI	-2.1 (-15.6, 11.5), p= 0.758, not significant	
HDL-Sterols:		
Raw mean value (mg/dl)	48.9	55.0
Mean % Δ from baseline (SE)	5.5 (5.0)	2.2 (2.6)
95% CI for mean percent change[a]	(-4.7, 15.7)	(-3.2, 7.6)
Diff. from placebo in mean % Δ from base.(95% CI	-3.3 (-14.4, 7.8), p= 0.553, not significant	
Total Plant Sterols[g]:		
Raw mean value (mg/dl)	204.1	216.8
Mean % Δ from baseline (SE)	3.7 (4.8)	-8.7 (2.5)
95% CI for mean percent change[a]	(-6.2, 13.5)	(-13.9, -3.5)
Diff. from placebo in mean % Δ from base.(95% CI	-12.4 (-23.1, -1.7), p= 0.025	
Non-HDL-Sterols:		
Raw mean value (mg/dl)	155.1	161.8
Mean % Δ from baseline (SE)	3.2 (8.0)	-10.2 (4.2)
95% CI for mean percent change[a]		
Diff. from placebo in mean % Δ from base.(95% CI	-13.4 (-31.2, 4.3), p= 0.133	
Total Cholesterol:		
Raw mean value (mg/dl)	144.6	168.0
Mean % Δ from baseline (SE)	8.0 (6.1)	-4.8 (3.2)
95% CI for mean percent change[a]		
Diff. from placebo in mean % Δ from base.(95% CI	-12.8 (-26.4, 0.7), p= 0.063	
Triglycerides:		
Median value (mg/dl)	195.0	147.5
Median % Δ from baseline (SE)	-20.8 (6.9)	-2.1 (8.1)
95% CI for **median** percent change[a]	(-37.6, -4.0)	(-18.7, 14.6)
Diff. from placebo in **median** % Δ from base.[c]	-18.7, p= 0.498= not significant	
Apo A-1:		
Raw mean value (mg/dl)	146.7	159.0
Mean % Δ from baseline (SE)	0.6 (4.2)	6.5 (2.2)
95% CI for mean percent change[a]	(-7.9, 9.2)	(2.0, 11.0)
Diff. from placebo in mean % Δ from base.(95% CI	5.9 (-3.4, 15.2), p= 0.207, not significant	
Apo B:		
Raw mean value (mg/dl)	128.2	129.9
Mean % Δ from baseline (SE)	3.1 (4.5)	-12.7 (2.4)
95% CI for mean percent change[a]	(-6.1, 12.2)	(-17.5, -7.9)
Diff. from placebo in mean % Δ from base.(95% CI	-15.8 (-25.8, -5.8), p= 0.003	

a= mean and standard error are LS Mean and LS Standard Error based on the ANOVA model
b= for LDL-C, medians were presented due to significant non-normality of the data
c= p-value for between-treatment difference based on nonparametric ANOVA using Turkey's normalized ranks
d= the sponsor analyzed the percent change in plasma concentration of LDL-C from baseline to endpoint by baseline LDL-C and stratum. This analysis demonstrated that, in patients who were randomized to ezetimibe and who had a baseline LDL-C ≤median value of 93.9 mg/dl (n= 14) had a median change of -1.5%, while those with values > median (n= 15), had a median change of -17.3%. Subjects on resins who were randomized to ezetimibe (n= 8) showed a median 2.9% increase in LDL-C while on ezetimibe and subjects not on resins (n= 21) showed a median –17.0% change in LDL-C
e= LDL-sterols= Total sterols – (HDL-sterols + TG/5)
f= the maximum reduction in LDL-sterols was seen at week 4 and maintained for the remainder of the study
g= Total sterols= cholesterol + plant sterols; note that the mean decrease from baseline in plasma total sterols is near maximal by week 2

Comment on the above table:

A statistically significant decrease in plasma campesterol levels occurred with ezetimibe therapy relative to baseline and to placebo. The difference between ezetimibe and placebo was also statistically significant for LDL-sterols, total plant sterols and Apo B.

The 1 subject receiving apheresis had a baseline plasma campesterol level of 2.4 mg/dl; the campesterol levels on weeks 2, 4, 6 and 8 were 2.0, 2.1, 2.6 and 1.8 mg/dl. The mean percent change in plasma campesterol level from baseline to endpoint (average of weeks 6 and 8) was –8.3% in this patient.

As with plasma sitosterol, the reduction in plasma campesterol was progressive over the 8-week treatment period in the modified intent-to-treat population:

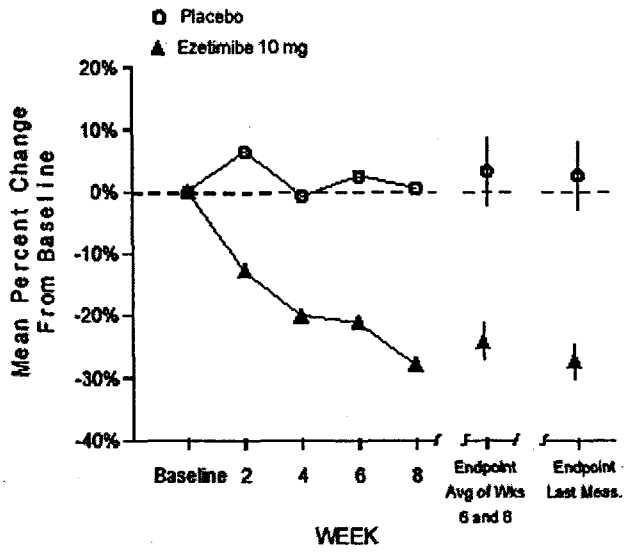

Figure 6 Mean percent change from baseline in plasma concentration of Campesterol over time and at endpoint in the 2 treatment groups: Modified Intent-to-Treat Population
Source Data: **Section 14.2.2.4.1.**

Exploratory Analysis:
At baseline, 3 subjects randomized to placebo and 12 randomized to ezetimibe had cutaneous xanthomas documented. The following table depicts the mean percent change in size of the largest cutaneous xanthoma directly measured at baseline and endpoint:

Percent Change in Cutaneous Xanthomas- Direct (cm^2) Between Baseline and Endpoint (Last Measurement): Intent-to-Treat Population)		
Xanthoma-Direct (cm^2)	Placebo (n= 3)	Ezetimibe (n= 12)
Baseline mean	2.4	2.1
Endpoint: Mean Mean % change from baseline (SE) 95% CI for mean percent change[a] Difference from placebo in mean percent change from baseline (95% CI)[a]	 2.7 -5.3 (6.3) (-19.0, 8.3)	 1.8 -9.0 (3.5) (-16.6, -1.5) -3.7 (-18.8, 11.4), p= 0.605
a= mean and standard error are LS Mean and LS Standard Error based on the ANOVA model		

At baseline, 6 subjects randomized to placebo and 18 randomized to ezetimibe had radiography performed to measure the thickness of the Achilles tendon. The following table depicts the mean percent change in xanthoma radiography between baseline and endpoint:

Percent Change in Xanthoma-Radiography (mm) Between Baseline and Endpoint (Last Measurement): Intent-to-Treat Population)		
Xanthoma-Radiography (mm)	Placebo (n= 6)	Ezetimibe (n= 18)
Baseline mean	15.7	18.2
Endpoint: Mean Mean % change from baseline (SE) 95% CI for mean percent change[a] Difference from placebo in mean percent change from baseline (95% CI)[a]	 16.8 8.0 (2.8) (2.2, 13.7)	 18.1 -0.6 (1.7) (-4.2, 3.0) -8.6 (-15.1, -2.0), p= 0.013
a= mean and standard error are LS Mean and LS Standard Error based on the ANOVA model Means only include subjects who had both baseline and endpoint xanthomas		

Reviewer's comment:
The small sample sizes limit the utility of these data and the ability to draw meaningful conclusions.

EFFICACY IN LONG-TERM, OPEN-LABEL EXTENSION STUDY: P00476:

Of the 1719 subjects who received randomized treatment assignment in the double-blind phase of P00474 and P00475, 1313 received treatment in P00476 (only 2 of these 1313 subjects did not complete the double-blind treatment phase of P00474/475). 783/1313 (59.6%) of subjects attained target LDL-C levels with ezetimibe alone; 530 (40.4%) did not, thus requiring the addition of statin therapy.

The number of subjects who were exposed to ezetimibe with or without statin in P00474/475/476 was 1,624 subjects (311 subjects who received ezetimibe in P00474/475 only plus the 1313 subjects enrolled in P00474/475/476). Of these 1,624 patients, 1288 received their first dose of ezetimibe in P00474/475 and 336 received their first dose of ezetimibe in P00476.

Of the 1624 subjects exposed to ezetimibe with or without statin in P00474/475/476, 530 received ezetimibe + statin and 1094 received only ezetimibe.

The following tables depict the effect of ezetimibe alone and of ezetimibe plus statin on LDL-C, HDL-C, TC and TG over time, relative to baseline. The tables are based on the number of subjects in whom a baseline and at least one post-baseline lipid measurement in P00476 was available as of the cut-off date of July 15, 2001

The Effect of Ezetimibe 10 mg Monotherapy on Calculated LDL-C, HDL-C, Total Cholesterol and Triglyceride Levels in Consecutive 3-Month Intervals Over 18 Months and at Endpoint, Relative to Baseline:

Interval	Calculated LDL-C Mean (SE)	HDL-C Mean (SE)	Total Cholesterol Mean (SE)	Triglyceride Mean (SE)
<3 months (n= 1602)[a]	(n= 1598)[b]	(n= 1602)[b]	(n= 1602)[b]	(n= 1602)[b]
Baseline (mg/dl)	165.66 (0.56)	52.12 (0.32)	251.67 (0.66)	169.94 (1.54)
% change	-18.51 (0.26)	0.84 (0.26)	-12.99 (0.20)	-4.60 (0.67)
3 to <6 mos. (n= 1229)[a]	(n= 1224)[b]	(n= 1229)[b]	(n= 1229)[b]	(n= 1229)[b]
Baseline (mg/dl)	165.28 (0.63)	52.39 (0.36)	251.48 (0.75)	169.54 (1.74)
% change	-18.22 (0.32)	0.36 (0.30)	-12.79 (0.24)	-3.13 (0.81)
6 to <9 mos. (n= 799)[a]	(n= 799)[b]	(n= 799)[b]	(n= 799)[b]	(n= 799)[b]
Baseline (mg/dl)	161.05 (0.68)	53.08 (0.46)	247.64 (0.86)	168.04 (2.15)
% change	-18.59 (0.38)	2.64 (0.41)	-12.41 (0.29)	-3.96 (0.99)
9 to <12 months (n= 685)[a]	(n= 682)[b]	(n= 685)[b]	(n= 685)[b]	(n= 685)[b]
Baseline (mg/dl)	159.86 (0.70)	53.17 (0.49)	246.32 (0.89)	166.98 (2.33)
% change	-19.74 (0.43)	3.16 (0.45)	-12.98 (0.33)	-3.86 (1.09)
12 to <18 months (n= 569)[a]	(n= 567)[b]	(n= 569)[b]	(n= 569)[b]	(n= 569)[b]
Baseline (mg/dl)	158.09 (0.73)	53.54 (0.54)	244.82 (0.94)	166.48 (2.58)
% change	-21.47 (0.49)	1.88 (0.50)	-14.53 (0.38)	-4.43 (1.22)
≥ 18 mos. (n= 4)[a]	(n= 4)[b]	(n= 4)[b]	(n= 4)[b]	(n= 4)[b]
Baseline (mg/dl)	178.83 (16.6)	47.17 (3.85)	266.83 (19.5)	203.83 (19.6)
% change	-43.63 (2.95)	16.63 (3.16)	-28.60 (2.41)	-14.83 (2.63)
Endpoint (Ez Momotherapy) (n= 1603)[a]	(n= 1600)[b]	(n= 1603)[b]	(n= 1603)[b]	(n= 1603)[b]
Baseline (mg/dl)	165.64 (0.56)	52.12 (0.32)	251.65 (0.66)	169.90 (1.54)
% change	-17.28 (0.31)	1.40 (0.29)	-11.95 (0.23)	-3.20 (0.73)

a= number of subjects for whom a baseline value was recorded;
b= number of subjects for whom a postbaseline value within the indicated interval was recorded;
Mean values are arithemetic means and SE= standard error

Comment on the above table:

In the subgroup of patients who were able to attain target LDL-C levels on ezetimibe alone, the effect of ezetimibe monotherapy in reducing LDL-C, TC, HDL-C and TG was maintained for up to 18 months of treatment.

The Effect of Ezetimibe 10 mg Monotherapy on Calculated LDL-C, HDL-C, Total Cholesterol and Triglyceride Levels in the Subjects Who Subsequently Received Statin Therapy:

Interval	Calculated LDL-C Mean (SE)	HDL-C Mean (SE)	Total Cholesterol Mean (SE)	Triglyceride Mean (SE)
Endpoint (n= 526)[a]	(n= 528)[b]	(n= 528)[b]	(n= 528)[b]	(n= 528)[b]
Baseline (mg/dl)	176.73 (1.06)	49.83 (0.54)	261.92 (1.21)	177.38 (2.67)
% change	-13.50 (0.45)	2.31 (0.48)	-9.75 (0.35)	-4.37 (1.16)

a= number of subjects for whom a baseline value was recorded;
b= number of subjects for whom a postbaseline value within the indicated interval was recorded;
Mean values are arithemetic means and SE= standard error

Comment on the above table:

In the subgroup of patients who required statin therapy to attain target LDL-C, the mean % change in LDL-C and TC from baseline to endpoint on ezetimibe therapy alone was -13.5% and -9.8%, respectively.

The Effect of Ezetimibe 10 mg Coadministered With Statin Therapy on Calculated LDL-C, HDL-C, Total Cholesterol and Triglyceride Levels in Consecutive 3-Month Intervals Over 18 Months and at Endpoint, Relative to Baseline:

Interval	Calculated LDL-C Mean (SE)	HDL-C Mean (SE)	Total Cholesterol Mean (SE)	Triglyceride Mean (SE)
<3 months (n=522)[a]	(n= 522)[b]	(n= 522)[b]	(n= 522)[b]	(n= 522)[b]
Baseline (mg/dl)	176.70 (1.06)	49.73 (0.54)	261.74 (1.22)	177.18 (2.67)
% change	-42.01 (0.54)	4.65 (0.51)	-30.03 (0.43)	-15.64 (1.25)
3 to <6 mos. (n= 403)[a]	(n= 402)[b]	(n= 403)[b]	(n= 403)[b]	(n=403)[b]
Baseline (mg/dl)	177.80 (1.20)	49.58 (0.61)	263.14 (1.38)	179.61 (3.00)
% change	-41.15 (0.62)	5.50 (0.65)	-29.38 (0.49)	-16.48 (1.23)
6 to <9 mos. (n=310)[a]	(n= 310)[b]	(n= 310)[b]	(n= 310)[b]	(n= 310)[b]
Baseline (mg/dl)	179.08 (1.43)	49.31 (0.65)	264.07 (1.66)	179.07 (3.24)
% change	-41.37 (0.69)	5.14 (0.90)	-29.84 (0.56)	-16.15 (1.61)
9 to <12 months (n= 216)[a]	(n= 215)[b]	(n= 216)[b]	(n= 216)[b]	(n= 216)[b]
Baseline (mg/dl)	181.59 (1.75)	48.44 (0.71)	266.25 (1.97)	181.52 (4.02)
% change	-41.54 (0.85)	4.94 (0.75)	-30.03 (0.68)	-15.45 (1.99)
12 to <18 months (n= 94)[a]	(n= 94)[b]	(n= 94)[b]	(n= 94)[b]	(n= 94)[b]
Baseline (mg/dl)	180.36 (2.83)	48.52 (1.03)	263.76 (3.07)	174.71 (5.56)
% change	-42.76 (1.24)	3.19 (1.28)	-31.84 (1.03)	-20.92 (2.66)
Endpoint (Ez + Statin) (n= 528)[a]	(n= 528)[b]	(n= 528)[b]	(n= 528)[b]	(n= 528)[b]
Baseline (mg/dl)	176.73 (1.06)	49.83 (0.54)	261.92 (1.21)	177.38 (2.67)
% change	-41.74 (0.56)	4.44 (0.56)	-29.93 (0.45)	-16.27 (1.19)

a= number of subjects for whom a baseline value was recorded;
b= number of subjects for whom a postbaseline value within the indicated interval was recorded;
Mean values are arithemetic means and SE= standard error

Comment on the above table:

The effect of coadministration of ezetimibe with either lovastatin or simvastatin on LDL-C, HDL-C, TC and TG was maintained for up to 18 months of treatment.

Comparison Between Ezetimibe Plus Lovastatin and Ezetimibe Plus Simvastatin for the Range in Mean Baseline and the Mean % Change From Baseline to Endpoint for LDL-C, HDL-C, TC and TG:

	LDL-C		HDL-C		Total Cholesterol		Triglcerides	
	Ez + Lova	Ez+Simva	Ez + Lova	Ez+Simva	Ez + Lova	Ez+Simva	Ez + Lova	Ez+Simva
Baseline (mg/dl)	(n= 192) 177.2	(n= 336) 176.3	(n= 192) 48.5	(n= 336) 505	(n= 192) 262.4	(n= 336) 261.5	(n= 192) 184.4	(n= 336) 173.6
Mean % Δ from base. to endpoint	-37.4	-44.2	3.6	4.9	-27.1	-31.6	-13.9	-17.6

Number of Subjects in Each Statin Group in Consecutive 3-Month Intervals Over 18 Months and at Endpoint:

	<3 months	3-<6 mos.	6-<9 mos.	9-<12 mos	12-<18mo	endpoint
Lova	192	165	153	111	46	192
Simva	330	238	157	105	48	336

Comment on the above table:
More subjects received simvastatin than lovastatin because the protocol was amended from randomized assignment to either statin to assignment only to simvastatin.

D. Efficacy Conclusions

The primary efficacy measurement in all but one (Sitosterolemia Study, P02243) of the 13 pivotal trials was plasma LDL-C. In the majority of studies, both direct LDL-C (measured by a [redacted] procedure) and calculated LDL-C (using the Friedewald equation) were determined. As expected, the results of the 2 methodologies were consistent since subjects with TG elevations above 350 mg/dl (which can interfere with the accuracy of the calculated measurement) were excluded. Since calculated LDL-C rather than direct LDL-C is widely used in clinical practice, the sponsor proposed this measure for use in the ezetimibe label. The primary prespecified efficacy variable in all Phase III studies (except Sitosterolemia) was percent change in LDL-C concentrations from baseline to study endpoint, using an intent-to-treat approach.

PHASE II STUDIES:

Three Phase II studies (C96-411/C96-345, C98-010 and C98-258) with treatment phases of 8 weeks or 12 weeks were included to support the selected therapeutic dose, 10 mg, the dose interval, once daily, and the timing of dose administration, AM or PM, for the Phase III studies. The study design in all of these three Phase II studies was a randomized, double-blind, placebo-controlled, parallel-group design. The Initial Dose-Ranging Study, C96-411/C96-345, compared the effects of ezetimibe to placebo at doses of [redacted] 10, [redacted] mg. Subjects were randomized to receive either placebo or 1 of these [redacted] doses of ezetimibe for 8 weeks (total sample size was

124 with 16-20 subjects/treatment group). The "Pivotal" Dose-Response Study, C98-010, tested the effects of a narrower range of ezetimibe doses, ——— and 10 mg, versus placebo in a larger group of subjects (total sample size was 243 with 46-52 subjects/treatment group) for a longer duration (12 weeks). In the Dose-Regimen Study, C98-258, the effect of morning vs. evening dosing with either ——— · 10 mg ezetimibe was evaluated in a total of 189 subjects (36-40 subjects/treatment group). In all three studies, the primary efficacy variable was the mean percent change from baseline to endpoint in plasma LDL-C concentrations.

Based on these efficacy results, ezetimibe 10 mg/day was selected for investigation in the Phase III program for the following reasons:
-Ezetimibe monotherapy at doses —mg/day resulted in mean percent reductions in plasma LDL-C concentrations that were consistently <15%. Higher doses, ——— mg, produced reductions ranging from 15-20%;
-Ezetimibe monotherapy at doses >10 mg/day (up ——mg/day) did not promote significantly greater reductions in LDL-C concentrations relative to the 10 mg dose (i.e. a plateauing trend was observed). Specifically, at 10 mg/day, the mean changes ranged from –16.4% to –18.7%. Doses >10 mg resulted in an increase in response that was small relative to the increase in dose. At —mg/day, the highest dose tested, mean changes in plasma LDL-C concentrations were –20%; and
-In an analysis of pooled results from the two 12-week studies, C98-010 and C98-258, significantly greater reductions in plasma LDL-C were observed with the 10 mg dose than with the —mg dose. Moreover, among all treated subjects in C96-411/C96-345, C98-010 and C98-258, 67% receiving the 10 mg dose exhibited at least a 15% reduction in LDL-C versus 51% receiving the — mg dose.

In addition, in these 3 studies, maximal or near-maximal effects on LDL-C lowering were observed at week 2 and continued for the 8-12 weeks study duration. Also, the timing of dosing with ezetimibe, either before a morning meal or at bedtime, had no effect on response to treatment.

PHASE III STUDIES:
All efficacy analyses reported in this review are for the Intent-to-Treat Population unless otherwise stated.

Monotherapy (P00474 and P00475):
1,719 subjects with primary hypercholesterolemia were randomized to placebo (n= 431) or to ezetimibe (n= 1,288) for 12 weeks in two phase III trials.

In the pooled Phase III Monotherapy Studies, treatment with ezetimibe 10 mg reduced plasma concentrations of the following lipid variables relative to baseline: direct LDL-C, 17.4%; calculated LDL-C, 18.2%; TC, 12.7%, TG, 4.2% (this was mean; median was –8.0%) and Apo B, 15.7% and increased HDL-C by 1.0%. The corresponding mean changes in the ezetimibe group relative to the placebo group were-17.7% for direct LDL-C, -19.1% for calculated LDL-C, -13.1% for TC, -7.8% for TG, -14.1% for Apo B and +2.6% for HDL-C (all p values were $\leq$ 0.01).

By study, only the difference between ezetimibe and placebo for calculated and direct LDL-C, TC and Apo B were statistically significant at the $p \leq 0.01$ level for each study. For HDL-C, the additional rise observed with ezetimibe compared to placebo was significant at the $p \leq 0.01$ level only for study P00475 (additional 2.9% increase). For study P00474, ezetimibe produced an additional 2.3% increase in HDL-C, which was significant at the $p \leq 0.05$ level. For TG, the difference between ezetimibe and placebo was statistically different in study P00475 only (P00475: - 11.4%, $p \leq 0.01$; P00474: -4.1%, $p= 0.09$, not significant).

The changes in LDL-C occurred as early as week 2 and were maintained for the 12-week study duration.

Subgroup analysis of the individual monotherapy studies generally showed consistency of treatment effect across all subgroups examined. Of note, only in study P00475 was a treatment-by-race interaction observed (see Section IX.B. for details).

Factorial Coadministration Studies (P00679, P00680, P00691 and P00692):
2,382 subjects with primary hypercholesterolemia were enrolled in 4 randomized, placebo-controlled 12-week studies to evaluate the efficacy and safety of ezetimibe coadministered with either lovastatin, simvastatin, pravastatin or atorvastatin. 259 subjects were randomized to placebo, 262 to ezetimibe, 936 to statin alone (220 subjects to lovastatin, 263 to simvastatin, 205 to pravastatin and 248 to atorvastatin) and 925 to ezetimibe + statin (192 subjects to coadministration with lovastatin, 274 to coadministration with simvastatin, 204 to coadministration with pravastatin and 255 to coadministration with atorvastatin).

In each of the Factorial Coadministration Studies, the primary efficacy analysis was the difference in mean percent change in plasma LDL-C for the following groups:
pooled ezetimibe + statin group (pooled for all doses of a given statin) vs. pooled statin alone group (pooled for all doses of a given statin) AND
pooled ezetimibe + statin group (pooled for all doses of a given statin) vs.ezetimibe alone group for a given study.
The observed differences represent the incremental LDL-C lowering attributable to ezetimibe.

RESULTS:
Additional Change in Lipid Variables With Coadministration Compared to Statin Alone And To Ezetimibe Alone, Across All Doses of a Given Statin:
LDL-C:
In the individual studies, the differences in the above treatment groups for LDL-C were statistically significant ($p < 0.01$). The observed incremental reduction in calculated LDL-C with coadministration, all doses of a given statin pooled, compared to the corresponding statin alone, all doses pooled, ranged from -12.1 to –15.0%. The incremental reduction in LDL-C with coadministration compared to ezetimibe alone ranged from –19.0 to –36.4% in the 4 Factorial Studies.

TC, TG, HDL-C and Apo B:

The incremental change in TC, TG and Apo B with coadministration compared to statin alone or to ezetimibe alone was statistically significant ($p \leq 0.01$) for each factorial study. Compared to statin alone, coadministration yielded an additional 9.1 to 10.8% lowering in TC, 7.4 to 10.5% lowering in TG and 9.3 to 12.3% lowering in Apo B. Compared to ezetimibe alone, the additional decreases were 13.9 to 27.6% for TC, 15.5 to 26.0% for TG and 15.4 to 30.0% for Apo B.
The difference between pooled coadministration and pooled ezetimibe for HDL-C was statistically significant ($p \leq 0.05$) for all 4 statins studied, ranging from +3.1 to +5.1%. However, the increase in HDL-C with coadministration compared to statin alone was statistically significant for only 3 of the 4 factorial studies, lovastatin, simvastatin and atorvastatin, +2.4 to +4.5%, $p \leq 0.05$. The +1.4% increment for coadministration with pravastatin compared to pravastatin aone was not statistically significant.

Cholesterol Ratios: direct LDL-C/HDL-C and TC/HDL-C:
As a consequence of the observed incremental reductions in LDL-C and TC concentrations, in conjunction with incremental increases in HDL-C, ezetimibe/statin coadministration resulted in favorable reductions in the ratios of LDL-C/HDL-C and TC/HDL-C compared to statin alone.

Dose-by-treatment interaction:
Although a statistically significant dose-by-treatment interaction was noted in the simvastatin factorial study at endpoint for the intent-to-treat data set, this finding was attributable to anomalous values at endpoint for the low-to-mid dose range. These irregularities were not apparent at earlier time points, and even at endpoint did not result in a significant interaction in the protocol-evaluable analysis. Thus, the average effect across all doses still provided the best estimate of overall ezetimibe effect when coadministered with simvastatin.

Additional Change in Lipid Variables With Coadministration Compared to Statin Alone And To Ezetimibe Alone, Across All Doses of All Statins:
Across all doses of all statins, coadministration yielded an additional 13.8% reduction in calculated LDL-C compared to statin alone and an additional 27.3% reduction compared to all ezetimibe alone. The corresponding additional decreases for TC were, respectively, 10.2% and 20.2%; for TG, 9.0% and 19.0%; and for Apo B, 10.7% and 22.9%. The corresponding additional increases for HDL-C were 2.9% and 4.1%, respectively.

Additional Change in Lipid Variables With Coadministration Compared to Statin Alone And To Ezetimibe Alone, By Statin, By Dose (i.e. Individual Treatment Group Comparisons):
With the exception of ezetimibe + atorva 40 mg vs. atorva 80 mg, the incremental mean percent change in LDL-C and TC observed when ezetimibe was administered with any given statin dose was significantly greater ($p \leq 0.01$) than the corresponding or next higher dose of that statin administered alone. In general, this was also true for Apo B but not for TG or HDL-C.

In addition, coadministration of ezetimibe with the lowest dose of statin studied, 10 mg, resulted in LDL-C and TC concentrations similar to that seen with the highest dose tested of statin alone.

In general, the incremental effect of coadministration compared to statin alone on LDL-C reduction was independent of the dose or specific statin.

Time to Therapeutic Response:
The LDL-C lowering effects for all active treatments was seen as early as week 2 and was maintained for the 12 week study duration.

Comparison of Placebo and Ezetimibe Treatment Arms in the Phase III Monotherapy and Factorial Coadministration Studies:
Comparison of the 2 pooled phase III monotherapy trials (P00474 + P00475) to the placebo and ezetimibe treatment arms of the 4 pooled factorial studies (P00679 + P00680 + P00691 + P00692) demonstrated comparable changes in the primary and key secondary lipid variables:

	[Ez – Placebo] for Mean % Change From Baseline to Endpoint	
	Pooled Monotherapy Studies	Pooled Factorial Studies
Direct LDL-C	-17.7%	-19.9%
Calculated LDL-C	-19.1%	-20.0%
TC	-13.1%	-14.1%
TG	-7.8%	-7.4%
Apo B	-14.1%	-15.0%
HDL-C	+2.6%	+2.7%

In each of these 6 studies, the difference between ezetimibe and placebo was statistically significant at the $p \leq 0.01$ level for direct and calculated LDL-C, TC and Apo B. For TG, this difference was statistically significant ($p \leq 0.01$) for studies P00475 and P00680 (simvastatin) only, with ezetimibe yielding an additional 11-12% reduction in TG lowering compared to placebo. For HDL-C, the additional rise in HDL-C with ezetimibe compared to placebo was statistically significant ($p \leq 0.05$) for studies P00474 (2.3%), P00475 (2.9%), P00679 (lovastatin, 3.8%) and P00680 (simvastatin, 4.3%) only.

Subgroup Analysis:
The results of the subgroup analyses in the pooled Factorial Coadministration Studies showed generally consistency across all subgroups examined for the LDL-C response to treatment with the exception of an observed race difference to coadministration therapy between Caucasians and Non-Caucasians. In the pooled Factorial Studies, the treatment difference between coadministration and statin alone for the mean LDL-C reduction from baseline to endpoint, was –14.6% for Caucasians (n= 803) and –6.6% for Non-Caucasians (n= 111). Additional subgroup analyses demonstrated that this treatment difference was predominately due to a diminshed LDL-C response to coadministration therapy in Asian (n= 18) and Black (n= 44) subjects. This was particularly evident in the atorvastatin factorial study, in which the treatment difference between ezetimibe/atorva and atorva alone in the mean percent change in LDL-C from baseline to endpoint was ~+15% and ~+5% in Black (n= 9) and Asian (n= 6) subjects, respectively, compared to a mean change of -13% in Caucasians (n= 222) enrolled in this study. Additional subgroup analyses demonstrated diminished mean LDL-C response over time in Black and Asian subjects receiving coadministration therapy (in Blacks: for the pooled Factorial Studies, atorvastatin and simvastatin factorial studies; in Asians: for the pooled Factorial Studies, atorvastatin and pravastatin factorial studies). The small number of Non-Caucasian subjects

enrolled in these studies confounds interpretation of these findings. Note that clinical studies, in general, are not powered to detect differences in subgroup results. (Please refer to Section IX.B. for details).

Add-On Study (P02173):
The study population consisted of 769 subjects who had been taking an approved statin at a stable dose for at least 6 weeks and who had not met their NCEP ATP II LDL-C target. A large percentage of these subjects had established CHD or diabetes mellitus, justifying a target LDL-C of $\leq$100 mg/dl. 379 subjects were randomized to 8 weeks of blinded therapy with ezetimibe 10 mg/day or matching placebo, taken in addition to ongoing treatment with the same open-label statin they were using at baseline.

The addition of ezetimibe to ongoing statin therapy resulted in an additional mean reduction from baseline in plasma LDL-C level of 21.5% compared with placebo plus statin ($p < 0.001$). The magnitude of the additional LDL-C reductions were consistent across the different statins: atorvastatin, -21.0%; simvastatin, -23.7%; and all other statins (pravastatin, fluvastatin, lovastatin and cerivastatin), -19.7%. Maximal or near-maximal effects on LDL-C concentrations occurred within 2 weeks of initiation of ezetimibe dosing, and were maintained throughout the duration of the study.

With regard to key secondary efficacy variables, the addition of ezetimibe to ongoing statin therapy further reduced TC and TG by 14.7% and 11.1%, respectively relative to placebo plus statin ($p < 0.001$). The additional increase in HDL-C was small, 1.7%, but statistically significant ($p < 0.05$).

Except for Apo A-1, a significant treatment difference ($p < 0.05$) was observed between the two treatment groups for all the other secondary efficacy variables which included non-HDL-C, Apo B, Apo A-II, LDL-C/HDL-C, TC/HDL-C and CRP.

A key secondary analysis was the percentage of subjects who achieved NCEP ATP II LDL-C targets at study endpoint. For the group in which ezetimibe was added to a statin, 76% of subjects achieved target LDL-C at endpoint compared with 27% in the placebo plus statin group. Since the study inclusion criteria made it possible for some subjects who were near their LDL-C target to be entered, some participants were already "at target" at baseline. Excluding those near target, the % of subjects achieving goal at endpoint was 72% for the ezetimibe group vs. 19% for the placebo group.

With the exception of race, the results of the subgroup analysis indicated that the response to ezetimibe 10 mg added to ongoing statin therapy was generally consistent across subgroups. However, ezetimibe added to ongoing statin therapy resulted in an additional 22.0% lowering of LDL-C in Caucasians (n= 336) compared to an additional 15.3% in Non-Caucasians (n= 39). Per the statistical reviewer, Dr. Japo Choudhury, the p-value for the race difference was 0.056. (Please refer to Section IX.B. for details). Diminished LDL-C response to coadministration therapy over time was evident in the Black (n= 27), Asian (n= 5) and Hispanic (n= 8) groups. As

with the other studies, the small number of non-Caucasians enrolled in this study confounds interpretation of the data.

Familial Homozygous Hypercholesterolemia (FHH or HoFH) (P01030):
The study population consisted of 50 subjects with FHH, aged 11-74 years, with elevated levels of calculated LDL-C (≥ 100 mg/dl) on atorvastatin or simvastatin 40 mg. They were randomized 2:1 ezetimibe + statin (atorvastatin or simvastatin) 40/80 mg (n= 33) to statin (atorvastatin or simvastatin) 80 mg (n= 17) for 12 weeks of double-blind treatment. The cohort included subjects being treated concurrently with LDL apheresis and, in 2 subjects, with bile acid binding resins. Note that the **daily dose of study drug was to be taken at least 4 hours before or after administration of the resin. This provision was included because of evidence that an interaction between ezetimibe and resins resulted in reduced uptake and efficacy of ezetimibe.**

In subjects with FHH, ezetimibe 10 mg/day added to therapy with simvastatin or atorvastatin 40/80 mg produced statistically significantly greater incremental reductions in plasma LDL-C ($p= 0.007$) and TC ($p< 0.01$) concentrations compared with increasing simvastatin or atorvastatin monotherapy from 40 to 80 mg. The difference in mean percent change from baseline to endpoint in the ez + statin 40/80 mg group relative to the statin 80 mg group was ~14% for LDL-C (14.1% for direct LDL-C and 14.8% for calculated LDL-C) and, was ~13% for TC. Comparison of the high dose groups demonstrated that ezetimibe plus statin 80 mg produced an additional reduction in LDL-C of -20.5% ($p= 0.0001$) and TC of -18.1% ($p< 0.01$) compared with statin 80 mg alone.

The LDL-C lowering effect of ezetimibe coadministered with statin 40/80 mg was seen as early as week 2 and was maintained for the duration of the study.

It should be noted that there were no significant differences between ezetimibe + statin 40/80 mg and statin 80 mg nor between ezetimibe + statin 80 mg vs. statin 80 mg in the mean percent changes from baseline in the plasma concentrations of TG, Apo B and HDL-C. It should also be noted that ezetimibe exerted a 2-3% lowering effect on HDL-C in this patient population compared to an ~4% increase with placebo.

An open-label, up to 24-month extension study, P01417, is ongoing to primarily evaluate the safety and tolerability of ezetimibe 10 mg coadministered with atorvastatin or simvastatin in patients with FHH. For P01417, an interim safety report was submitted to the NDA; efficacy was not analyzed in this interim report.

Homozygous Sitosterolemia (P02243):
The study population consisted of 37 subjects, 24 women and 13 men, aged 9-72 years with homozygous sitosterolemia who had continued elevations of plasma sitosterol (>5 mg/dl) on their current therapeutic regimen. Subjects were randomized 4:1, ezetimibe 10 mg (n= 30) to placebo (n= 7) for 8 weeks. **Due to *in vitro* and *in vivo* data demonstrating a drug interaction between ezetimibe and bile salt binding resins (BSBR), the protocol was amended to either reduce or discontinue BSBR therapy, if clinically appropriate. If this change was not**

deemed appropriate, ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered.

8 weeks of daily treatment with ezetimibe 10 mg reduced plasma concentrations of sitosterol and campesterol relative to baseline and to placebo. Specifically, treatment with ezetimibe resulted in a mean change in plasma sitosterol concentrations from baseline to endpoint of –21% compared with a mean change of +4% in the placebo group, yielding a between-group difference of –25% ($p < 0.001$). The corresponding changes for campesterol were ~24% mean reduction with ezetimibe therapy; ~3% mean increase on placebo; yielding a between-group difference of ~ -27% ($p < 0.001$).

Subgroup analysis showed that in subjects receiving ezetimibe, the reduction in sitosterol concentrations was similar between those who received concomitant bile-acid-binding resins and those who did not. A similar observation was made in subjects taking or not taking statins. However, these subgroups are small, limiting the interpretation of these findings.

Significant reductions in plasma concentrations of both sitosterol and campesterol occurred at week 2 and were progressive over the 8-week treatment period.

Treatment with ezetimibe also significantly reduced ($p< 0.05$) plasma LDL-sterols, total plant sterols and Apo B concentrations.

It should be noted that ezetimibe did not significantly differ from placebo in effects on LDL-C, TC, TG and HDL-C.

An extension study is ongoing to evaluate possible progressive changes in xanthoma size over longer periods of therapy, as well as to determine the [redacted] at steady-state with long-term therapy.

No epidemiological studies nor prospective clinical outcome studies are available to help assess the clinical impact of the reductions in plant sterols observed with ezetimibe treatment in this study although limited data from the cases reported in the literature suggest that this may be the case.

Efficacy in Long-Term, Open-Label Extension Study (P00476):
This study is an ongoing, 24-month extension study of the 12-week monotherapy studies, P00474 and P00475. Unlike P00474 and P00475 where patients were randomized to placebo or ezetimibe and the double-blind maintained for the duration of the study, in P00476, therapy with ezetimibe $\pm$ statin was open-label and titrated to NCEP ATP II target LDL-C levels. Patients not achieving their LDL-C goal with ezetimibe alone after one month, additionally received lovastatin or simvastatin. The statin dose could be titrated by pre-specified amounts and intervals up to 40 mg for lovastatin and 80 mg for simvastatin.

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1,624 subjects received treatment with ezetimibe with or without statin in P00474/475/476 as of the cut-off date for data analysis, July 15, 2001. Of these 1,624 subjects, 1,094 received treatment with ezetimibe alone and 530 received ezetimibe coadministered with statin. Over 550 subjects had data between 12 and 18 months. Only 4 subjects had data beyond 18 months.

Of these 1,624 subjects, 1,313 received treatment with ezetimibe with or without statin in P00476. 530 of these 1,313 subjects (40.4%) did not achieve target LDL-C level, and, therefore, required treatment also with statin.

Among the 1313 subjects who continued into the open-label extension and received treatment, 569 remained on ezetimibe monotherapy for a cumulative duration of 12 months or longer. The observed mean percent change from baseline in LDL-C in this group, as of the last measurement in the 12- to <18-month period, was –21.5% in conjunction with a decrease in TC of –14.5% and TG of –4.4% and an increase in HDL-C of +1.9%. Although these changes are consistent with those observed after 3-months of double-blind ezetimibe monotherapy, caution is recommended in comparing the results obtained in the long-term study to those in the 12- week studies due to different study designs (open-label vs. placebo-control) and objectives (titration of therapy to LDL-C goal vs. double-blind treatment with a fixed dose).

In subjects requiring the addition of statin therapy to achieve their LDL-C goal, the effect of coadministration of ezetimibe with either lovastatin or simvastatin on LDL-C, HDL-C, TC and TG was maintained for up to 18 months of treatment. The mean percent change from baseline in the 12- to <18 month period was –43% for LDL-C, -32% for TC, -21% for TG and +3% for HDL-C.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Dr. Bruce Stadel was the medical officer who reviewed the safety data submitted in this NDA. For information under this section, please refer to his review for an analysis of the safety data.

B. Description of Patient Exposure

C. Methods and Specific Findings of Safety Review

D. Adequacy of Safety Testing

E. Summary of Critical Safety Findings and Limitations of Data

VIII. Dosing, Regimen, and Administration Issues

The dosing regimen for ezetimibe was identified in the Phase II studies as 10 mg administered orally once daily.

Daily doses [redacted] mg produced mean reductions in direct LDL-C of <15% from baseline to endpoint. At [redacted] mg/day, ezetimibe produced mean changes ranging from -13.8% to -16.7% across the 3 studies. At 10 mg/day, the mean changes ranged from –16.4% to –18.7%. Doses >10 mg resulted in an increase in response that was small relative to the increase in dose. At [redacted] mg/day, the highest dose tested, mean changes in plasma LDL-C concentrations were –20%.

Food did not affect the oral bioavailability of ezetimibe.

Please refer to the Executive Summary, II.D. and II.E. which address dosing issues in Special Populations.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Gender effects were not demonstrable in the completed Phase III clinical studies. However, it should be noted that sample sizes by gender were small for the HoFH and Sitosterolemia studies and that clinical studies are not generally powered to detect differences in subgroup results.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Subgroup Analyses of Interest:

Monotherapy Studies: P00474 and P00475:

Subgroup analyses for direct LDL-C % change from baseline at endpoint were evaluated for the following: