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Editor's Choice

Safety profile of statins alone or combined with ezetimibe: a pooled analysis of 27 studies including over 22,000 patients treated for 6–24 weeks

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Disclosure
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SUMMARY

Aims: The aim of this analysis was to assess the overall safety and tolerability profiles of various statins + ezetimibe vs. statin monotherapy and to explore tolerability in sub-populations grouped by age, race, and sex. **Methods:** Study-level data were combined from 27 double-blind, placebo-controlled or active-comparator trials that randomized adult hypercholesterolemic patients to statin or statin + ezetimibe for 6–24 weeks. In the full cohort, % patients with AEs within treatment groups (statin: $N = 10{,}517$; statin + ezetimibe: $N = 11{,}714$) was assessed by logistic regression with terms for first-/second-line therapy (first line = drug-naïve or rendered drug-naïve by washout at study entry; second line = ongoing statin at study entry or statin run-in), trial within first-/second-line therapy, and treatment. The same model was fitted for age (< 65, ≥ 65 years), sex, race (white, black, other) and first-/second-line subgroups with additional terms for subgroup and subgroup-by-treatment interaction. **Results:** In the full cohort, the only significant difference between treatments was consecutive AST or ALT elevations ≥ 3 × upper limit of normal (ULN) (statin: 0.35%, statin + ezetimibe: 0.56%; $p = 0.017$). Significantly more subjects reported ≥ 1 AE; drug-related, hepatitis-related and gastrointestinal-related AEs; and CK elevations ≥ 10 × ULN (all $p \leq 0.008$) in first-line vs. second-line therapy studies with both treatments. AEs were generally similar between treatments in subgroups, and similar rates of AEs were reported within age and race subgroups; however, women reported generally higher AE rates. **Conclusions:** In conclusion, in second-line studies, ongoing statin treatment at study entry likely screened out participants for previous statin-related AEs and tolerability issues. These results describe the safety profiles of widely used lipid-lowering therapies and encourage their appropriate and judicious use in certain subpopulations.

What's known
The general safety and tolerability profiles of statin monotherapy and statin + ezetimibe combination therapy have been established. Comparable safety and tolerability profiles have been reported in subgroups by sex, race and age, although these secondary analyses have not been powered to assess statistical differences. Some cases of myopathy and rare cases of rhabdomyolysis have been reported during treatment with statins and ezetimibe.

What's new
The general safety and tolerability profiles of statin monotherapy and statin + ezetimibe combination therapy were confirmed. Irrespective of treatment group, generally higher rates of AEs were reported in women vs. men, and generally similar rates of AEs were reported between races and between age groups. More AEs were reported in first-line studies vs. second-line studies. The occurrence of myopathy was low and did not differ between treatments or any of the subgroups studied.

Introduction

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines recommend a low-density lipoprotein cholesterol (LDL-C) goal < 100 mg/dl (2.59 mmol/l) for high-risk patients (those with clinical cardiovascular disease, diabetes, or 10-year coronary heart disease [CHD] risk > 20%) and suggest an optional LDL-C goal < 70 mg/dl (1.81 mmol/l) for those at the highest risk, including those with established cardiovascular disease plus additional high-risk characteristics such as diabetes mellitus, multiple cardiovascular risk factors, and/or metabolic syndrome (1). In order to achieve LDL-C < 100 mg/dl (2.59 mmol/l) the majority of moderately high- and high-risk patients will need high-dose statin or a combination of statin and another lipid-lowering agent [reviewed in Ref. (2)]. Furthermore, in order to achieve an LDL-C < 70 mg/dl (1.81 mmol/l), almost all very high-risk patients will need high-dose statin or a combination of statin and another lipid-lowering agent [reviewed in Ref. (2)]. Advantages of using combination therapy include greater efficacy through differing mechanisms of action, lower doses of individual drugs, and potential amelioration of side effects expe-

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rienced with high doses of single agents. The potential disadvantages of combination therapy include drug interactions, increased number of pills, greater cost, and additive side effects. Moreover, data on clinical outcomes with combination therapy are limited.

The general safety and tolerability profiles of statin monotherapy and statin + ezetimibe combination therapy have been established in multiple clinical trials [reviewed in Refs (3,4)]. Cases of myopathy and rare cases of rhabdomyolysis have been reported during treatment with statins (5) and ezetimibe (6). With statins, these cases can occur at any dose level, but the risks increase at the higher doses and with certain concomitant medications (7–11). Clinical trials that have assessed lipid-lowering treatments are generally not powered to identify small between-treatment differences in safety and tolerability or rare adverse experiences. Moreover, conclusions drawn about differences in subpopulations, such as those assessed by age, race and sex, have been limited due to group size. The objective of this analysis was to assess the overall safety and tolerability profiles of various statins + ezetimibe vs. statin monotherapy and to explore tolerability in sub-populations grouped by age, race, and sex in a population of over 22,000 patients using pooled data combined from previously published trials.

Methods

In this analysis, study-level data were combined from 27 double-blind, placebo-controlled or active-comparator studies conducted between 1999 and 2008 by Merck Research Laboratories. In these studies adult hypercholesterolemic patients were randomized to statin or statin + ezetimibe for 6–24 weeks (Table 1) with a mean follow up duration of 9 weeks. Included studies were relatively short-term, lipid-lowering trials. Studies with cross-over design, extension studies, studies still ongoing, imaging studies, studies in which ezetimibe was used as monotherapy or in combination with other non-statin lipid-lowering drugs (e.g., fenofibrate, niacin), adolescent or pediatric patient studies, and studies focusing on patients with sitosterolemia, homozygous familial hypercholesterolemia, aortic stenosis, or chronic kidney disease were not included in these analyses.

Specific inclusion criteria for the individual studies have been previously published (see citations in Table 1). Since guidelines have changed over time, there was no single lipid entry criterion that applied to all studies. Generally, a patient was considered hypercholesterolemic if LDL-C levels were above guideline-recommended levels according to risk. The range of baseline LDL-C inclusion levels in the studies was between 70 mg/dl (1.81 mmol/l) to 250 mg/dl (6.47 mmol/l; Table 1).

Thirteen studies evaluated first-line therapy, which included subjects who were drug-naïve or rendered drug-naïve by wash-out at study start, and randomized patients to receive double-blind ezetimibe/statin [ezetimibe/simvastatin combination tablet (10/10, 10/20, 10/40, or 10/80 mg) or ezetimibe 10 mg co-administered with: simvastatin 10, 20, 40, or 80 mg; lovastatin 10, 20, or 40 mg; pravastatin 10, 20, or 40 mg or atorvastatin 10, 20, 40 or 80 mg] or statin alone (simvastatin 10, 20, 40, and 80 mg; lovastatin 10, 20, and 40 mg; pravastatin 10, 20, and 40 mg; atorvastatin 10, 20, 40, and 80 mg or rosuvastatin 10, 20, or 40 mg) for up to 12 weeks. There were 14 studies that evaluated second-line therapy, which included subjects who were previously on statins or receiving statins during run-in. In the add-on therapy studies (11 studies), statin-treated patients were randomized to receive double-blind placebo or ezetimibe 10 mg administered in combination with their ongoing, previously prescribed, open-label statin, which may have been doubled in some studies (simvastatin 10, 20, 40, or 80 mg; lovastatin 10, 20, or 40 mg; pravastatin 10, 20, or 40 mg; fluvastatin 20, 40, 80, or 160 mg; atorvastatin 10, 20, 40, or 80 mg or cerivastatin 0.2, 0.3, 0.4, or 0.8 mg) for up to 8 weeks. In ''switch-therapy'' studies (3 studies), statin-treated patients were switched from their ongoing, previously prescribed, open-label statin (simvastatin 10, 20, or 40 mg; lovastatin 10 or 20 mg; pravastatin 10 or 20 mg; fluvastatin 10 or 40 mg; atorvastatin 10, 20, or 40 mg or rosuvastatin 5 mg) to receive double-blind ezetimibe/statin (ezetimibe/simvastatin combination tablet 10/20 or 10/40 mg) or statin alone (simvastatin 20, 40, or 80 mg; lovastatin 20 or 40 mg; pravastatin 20 or 40 mg; fluvastatin 20 or 80 mg; atorvastatin 20, 40, or 80 mg or rosuvastatin 10 mg) for up to 24 weeks. Specific statin type and dose were matched between comparison groups in some trials, and in other trials, common-use comparisons were made (i.e., doses were compared that would frequently be used in a clinical setting, e.g. starting dose vs. starting dose, next higher dose vs. next-higher dose; Table 1).

Adverse experiences (AEs) were summarized by system organ class and specific adverse experience term. Prespecified safety parameters included alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) consecutive elevations $\geq 3 \times$ upper limit of normal (ULN); creatine kinase (CK) elevations $\geq 10 \times$ ULN; CK elevations $\geq 10 \times$ ULN with muscle symptoms (myopathy), and myopathy with associated evidence of renal damage (rhabdomyolysis). Special AEs of interest included hepatitis-related, gallbladder-related, gastrointestinal-related,

Table 1 Characteristics of studies included in the combined analyses

Protocol number (citation)	Treatment	Study duration	*n* of subjects who took statin (*N* = 10,387)	*n* of subjects who took statin + EZ (*N* = 11,891)	Inclusion criteria	
					Min LDL-C	Max LDL-C
005 (24)	EZ, PBO EZ + S 20, 40, 80 S 20, 40, 80	12 weeks	229	539	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
011 (25)	EZ, PBO S 10, 20, 40, 80 EZ + S 10, 20, 40, 80	12 weeks	263	274	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
021 (26)	EZ + S 20 S 40	24 weeks	110	104	101 mg/dl (2.62 mmol/l)	Not specified
023 (27)	S 20 EZ + S 20, 40, 80	23 weeks	253	457	130 mg/dl (3.37 mmol/l)	Not specified
025 (28)	A 10–80 EZ/S 10–80	24 weeks	262	526	Not at LDL-C goal as defined by NCEP ATP III	
030 (29)	EZ + A 10, 20, 40 A 10, 20, 40, 80	14 weeks	316	305	130 mg/dl (3.37 mmol/l)	Not specified
038 (30)	EZ, PBO EZ/S 10, 20, 40, 80 S 10, 20, 40, 80	12 weeks	622	609	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
040 (31)	EZ + ongoing statin Ongoing statin	6 weeks	1009	2009	Not at LDL-C goal as defined by NCEP ATP III	
051 (32)	EZ/S 20, 40, 80 A 10 20, 40, 80	6 weeks	947	948	Not at LDL-C goal as defined by NCEP ATP III	
058 (33)	EZ/S 20, 40, 80 R 10, 20, 40	6 weeks	1477	1474	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
077 (34)	EZ/S 20, 40 A 10, 20, 40	6 weeks	732	494	100 mg/dl (2.59 mmol/l)	Not specified
079 (35)	EZ + A 20 A 40	6 weeks	98	96	100 mg/dl (2.59 mmol/l)	160 mg/dl (4.14 mmol/l)
090 (36)	EZ + A 40 A 80	6 weeks	289	286	70 mg/dl (1.81 mmol/l)	160 mg/dl (4.14 mmol/l)
107 (37)	EZ/S 20, 40 A 10, 20, 40	6 weeks	678	450	70 mg/dl (1.81 mmol/l) 100 mg/dl (2.59 mmol/l)	Not specified
112 (38)	EZ + A 10 A 20/40	6 weeks	525	526	70 mg/dl (1.81 mmol/l)	160 mg/dl (4.14 mmol/l)
679 (39)	EZ, PBO L 10, 20, 40 EZ + L 10, 20, 40	12 weeks	220	192	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
691 (40)	EZ, PBO P 10, 20, 40 EZ + P 10, 20, 40	12 weeks	205	204	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
692 (41)	EZ, PBO A 10, 20, 40, 80 EZ + A 10, 20, 40, 80	12 weeks	248	255	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)
700 (42)	EZ S 20, 40	14 weeks	34	66	130 mg/dl (3.37 mmol/l)	Not specified
801 (43)	EZ + S 10, 20 S 10, 20	6 weeks	210	208	101 mg/dl (2.62 mmol/l)	160 mg/dl (4.14 mmol/l)
802 (44)	EZ + S 10, 20 S 10, 20	6 weeks	191	181	101 mg/dl (2.62 mmol/l)	160 mg/dl (4.14 mmol/l)
803/804 (45)	EZ + A 10, 20 A 10, 20	6 weeks	230	220	101 mg/dl (2.62 mmol/l)	160 mg/dl (4.14 mmol/l)
806 (46)	EZ/S 20 A 20	6 weeks	214	221	100 mg/dl (2.62 mmol/l)	160 mg/dl (4.14 mmol/l)
807 (47)	ES 20, 40 A 20	6 weeks	219	442	101 mg/dl (2.62 mmol/l)	160 mg/dl (4.14 mmol/l)
809 (48)	EZ/S 20 R 10	6 weeks	293	302	100 mg/dl (2.59 mmol/l)	160 mg/dl (4.14 mmol/l)
2173/2246 (49)	EZ + ongoing statin Ongoing statin	8 weeks	390	379	Not at LDL-C goal as defined by NCEP ATP III	
3377 (50)	EZ + S 20 S 20	12 weeks	123	124	145 mg/dl (3.75 mmol/l)	250 mg/dl (6.47 mmol/l)

A, atorvastatin; EZ, ezetimibe; L, lovastatin; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; P, pravastatin; R, rosuvastatin; S, simvastatin.

Table 2 Baseline characteristics for ITT population and subgroups included in analyses

ITT population

Parameter	Statin (*N* = 10,308)	Statin/EZ (*N* = 11,486)	Total (*N* = 21,794)
Male, *n* (%)	5279 (51.2)	6016 (52.4)	11,295 (51.8)
Female, *n* (%)	5029 (48.8)	5470 (47.6)	10,499 (48.2)
Mean age, years (SD)	59.2 (11.3)	59.9 (11.1)	59.6 (11.2)
< 65 years, *n* (%)	6682 (64.8)	7250 (63.1)	13,932 (63.9)
≥ 65 years, *n* (%)	3626 (35.2)	4236 (36.9)	5989 (36.1)
Caucasian, *n* (%)	8690 (84.3)	9706 (84.5)	18,396 (84.4)
Non-Caucasian, *n* (%)	1618 (15.7)	1780 (15.5)	3398 (15.6)
CHD, *n* (%)	3310 (32.1)	4115 (35.9)	7425 (34.1)
Diabetes mellitus, *n* (%)	3082 (29.9)	3459 (30.1)	6541 (30.0)
Metabolic syndrome, *n* (%)	4233 (50.7)	4518 (49.7)	8751 (50.1)
First-line, *n* (%)	6257 (60.7)	6241 (54.3)	12,498 (57.3)
Second-line, *n* (%)	4051 (39.3)	5245 (45.7)	9296 (42.7)
BMI ≥ 30 kg/m^2, *n* (%)	4138 (40.8)	4537 (40.1)	8675 (40.4)
BMI (kg/m^2)	(*n* = 10,143)	(*n* = 11,315)	(*n* = 21,458)
Mean (SD)	29.8 (5.9)	29.7 (5.8)	29.8 (5.8)

	Men		Women	
	Statin (*n* = 5279)	Statin/EZ (*n* = 6016)	Statin (*n* = 5029)	Statin/EZ (*n* = 5470)
Mean age, years (SD)	58.4 (11.2)	59.2 (11.1)	60.0 (11.2)	60.7 (11.0)
< 65 years, *n* (%)	3556 (67.4)	3909 (65.0)	3126 (62.2)	3341 (61.1)
≥ 65 years, *n* (%)	1723 (32.6)	2107 (35.0)	1903 (37.8)	2129 (38.9)
Caucasian, *n* (%)	4549 (86.2)	5187 (86.2)	4141 (82.3)	4519 (82.6)
Non-Caucasian, *n* (%)	730 (13.8)	829 (13.8)	888 (17.7)	951 (17.4)
CHD, *n* (%)	2129 (40.3)	2614 (43.5)	1181 (23.5)	1501 (27.5)
Diabetes mellitus, *n* (%)	1491 (28.2)	1732 (28.8)	1591 (31.6)	1727 (31.6)
Metabolic syndrome, *n* (%)	1912 (46.5)	2112 (45.8)	2321 (54.7)	2406 (53.6)
First-line, *n* (%)	3008 (57.0)	3081 (51.2)	3249 (64.6)	3160 (57.8)
Second-line, *n* (%)	2271 (43.0)	2935 (48.8)	1780 (35.4)	2310 (42.2)
BMI ≥ 30 kg/m^2, *n* (%)	1916 (36.8)	2206 (37.2)	2222 (45.0)	2331 (43.3)
BMI (kg/m^2)	(*n* = 5201)	(*n* = 5931)	(*n* = 4942)	(*n* = 5384)
Mean (SD)	29.3 (5.1)	29.4 (5.1)	30.3 (6.5)	30.1 (6.5)

	< 65 years		≥ 65 years	
	Statin (*n* = 6682)	Statin/EZ (*n* = 7250)	Statin (*n* = 3626)	Statin/EZ (*n* = 4236)
Mean age, years (SD)	52.8 (8.3)	53.3 (7.9)	70.9 (4.5)	71.3 (4.8)
Male, *n* (%)	3556 (53.2)	3909 (53.9)	1723 (47.5)	2107 (49.7)
Female, *n* (%)	3126 (46.8)	3341 (46.1)	1903 (52.5)	2129 (50.3)
Caucasian, *n* (%)	5451 (81.6)	5962 (82.2)	3239 (89.3)	3744 (88.4)
Non-Caucasian, *n* (%)	1231 (18.4)	1288 (17.8)	387 (10.7)	492 (11.6)
CHD, *n* (%)	1842 (27.6)	2189 (30.2)	1468 (40.5)	1926 (45.5)
Diabetes mellitus, *n* (%)	1897 (28.4)	2077 (28.6)	1185 (32.7)	1382 (32.6)
Metabolic syndrome, *n* (%)	2660 (49.0)	2734 (47.3)	1573 (53.8)	1784 (53.8)
First-line, *n* (%)	4555 (68.2)	4465 (61.6)	1702 (46.9)	1776 (41.9)
Second-line, *n* (%)	2127 (31.8)	2785 (38.4)	1924 (53.1)	2460 (58.1)
BMI ≥ 30 kg/m^2, *n* (%)	2910 (44.4)	3106 (43.6)	1228 (34.2)	1431 (34.1)
BMI (kg/m^2)	(*n* = 6553)	(*n* = 7124)	(*n* = 3590)	(*n* = 4191)
Mean (SD)	30.3 (6.2)	30.2 (6.1)	28.9 (5.1)	28.9 (5.1)

Table 2 (Continued)

	White		Black		Other	
	Statin (*n* = 8690)	**Statin/EZ (*n* = 9706)**	**Statin (*n* = 722)**	**Statin/EZ (*n* = 813)**	**Statin (*n* = 896)**	**Statin/EZ (*n* = 967)**
Mean age, years (SD)	59.7 (11.2)	60.3 (11.0)	56.0 (11.1)	57.7 (11.1)	56.4 (11.3)	57.3 (11.4)
< 65 years, *n* (%)	5451 (62.7)	5962 (61.4)	560 (77.6)	589 (72.4)	671 (74.9)	699 (72.3)
≥ 65 years, *n* (%)	3239 (37.3)	3744 (38.6)	162 (22.4)	224 (27.6)	225 (25.1)	268 (27.7)
Male, *n* (%)	4549 (52.3)	5187 (53.4)	303 (42.0)	319 (39.2)	427 (47.7)	510 (52.7)
Female, *n* (%)	4141 (47.7)	4519 (46.6)	419 (58.0)	494 (60.8)	469 (52.3)	457 (47.3)
CHD, *n* (%)	2894 (33.3)	3586 (37.0)	153 (21.2)	178 (22.0)	263 (29.4)	351 (36.3)
Diabetes mellitus, *n* (%)	2407 (27.7)	2631 (27.1)	285 (39.5)	377 (46.4)	390 (43.5)	451 (46.6)
Metabolic syndrome, *n* (%)	3532 (49.8)	3805 (49.0)	293 (53.9)	343 (56.7)	408 (56.4)	370 (50.8)
First-line, *n* (%)	5138 (59.1)	5183 (53.4)	527 (73.0)	523 (64.3)	592 (66.1)	535 (55.3)
Second-line, *n* (%)	3552 (40.9)	4523 (46.6)	195 (27.0)	290 (35.7)	304 (33.9)	432 (44.7)
BMI ≥ 30 kg/m^2, *n* (%)	3412 (39.9)	3756 (39.3)	407 (57.2)	482 (60.0)	319 (36.0)	299 (31.3)
BMI (kg/m^2)	**(*n* = 8546)**	**(*n* = 9557)**	**(*n* = 712)**	**(*n* = 804)**	**(*n* = 885)**	**(*n* = 954)**
Mean (SD)	29.7 (5.8)	29.6 (5.7)	32.2 (6.9)	32.4 (6.3)	29.0 (5.5)	28.4 (5.5)

	First-line		Second-line	
	Statin (*n* = 6257)	**Statin/EZ (*n* = 6241)**	**Statin (*n* = 4051)**	**Statin/EZ (*n* = 5245)**
Mean age, years (SD)	57.3 (10.9)	57.9 (10.7)	62.1 (11.2)	62.2 (11.1)
< 65 years, *n* (%)	4555 (72.8)	4465 (71.5)	2127 (52.5)	2785 (53.1)
≥ 65 years, *n* (%)	1702 (27.2)	1776 (28.5)	1924 (47.5)	2460 (46.9)
Male, *n* (%)	3008 (48.1)	3081 (49.4)	2271 (56.1)	2935 (56.0)
Female, *n* (%)	3249 (51.9)	3160 (50.6)	1780 (43.9)	2310 (44.0)
Caucasian, *n* (%)	5138 (82.1)	5183 (83.0)	3552 (87.7)	4523 (86.2)
Non-Caucasian, *n* (%)	1119 (17.9)	1058 (17.0)	499 (12.3)	722 (13.8)
CHD, *n* (%)	1019 (16.3)	1194 (19.1)	2291 (56.6)	2921 (55.8)
Diabetes mellitus, *n* (%)	1751 (28.0)	1569 (25.1)	1331 (32.9)	1890 (36.0)
Metabolic syndrome, *n* (%)	1364 (53.8)	1938 (55.5)	2869 (49.3)	2580 (46.0)
BMI ≥ 30 kg/m^2, *n* (%)	2685 (43.9)	2538 (41.6)	1453 (36.0)	1999 (38.3)
BMI (kg/m^2)	**(*n* = 6114)**	**(*n* = 6103)**	**(*n* = 4029)**	**(*n* = 5212)**
Mean (SD)	30.2 (6.1)	29.9 (5.9)	29.2 (5.5)	29.5 (5.7)

BMI, body mass index; CHD, coronary heart disease; EZ, ezetimibe; SD, standard deviation.

and allergic reaction or rash-related (see specific terms in footnote of Table 3). Safety populations were defined based on their definitions at the time of each individual study.

Laboratory AEs were analyzed in patients who had ≥ 1 post-baseline assessment; and special AEs of interest were analyzed in All Patients as Treated (APaT). In the full cohort, the percentage of patients with AEs within treatment groups was assessed by a logistic regression model with terms for first-line/second-line therapy (statin-naïve or rendered statin-naïve by washout/ongoing statin at study entry), trial within first-/second-line therapy, and treatment. The same model was fitted for age (< 65, ≥ 65 years), sex (male, female), race (white, black, other) and first-line/second-line subgroups with additional terms for subgroup and subgroup-by-treatment interaction. For rare AEs (those with a rate < 1% for both statin and statin plus ezetimibe treatments), the data were analyzed by a Poisson regression model. Due to the paucity of data, the trial within first-/second-line term coefficient could not be estimated in the Poisson regression model and was therefore excluded. For the full cohort, a sensitivity analysis was performed by way of risk difference using a logistic mixed model and Miettinen & Nurminen method with 'effective sample size'. The logistic mixed model included terms for first-/second-line study, treatment, and random effect for study.

Results

There were 10,542 patients randomized to the statin monotherapy groups and 11,746 subjects randomized

Table 3 Summary of safety data in the full cohort

	Statin	Statin/EZ	p-value for treatment
AE Summary, *n* (%)	**(*N* = 10,517)**	**(*N* = 11,714)**	
≥ 1 AE	3455 (32.85)	3717 (31.73)	0.547
Drug-related* AE	833 (7.92)	961 (8.20)	0.163
Serious AEs (SAEs)	145 (1.38)	187 (1.60)	0.202
Drug-related* SAEs	6 (0.06)	13 (0.11)	0.148
Death	5 (0.05)	7 (0.06)	0.700
Discontinuations			
Due to an AE	219 (2.08)	263 (2.25)	0.337
Due to drug-related* AE	136 (1.29)	177 (1.51)	0.133
Due to SAEs	34 (0.32)	38 (0.32)	0.899
Due to drug-related* SAEs	6 (0.06)	7 (0.06)	0.866
Laboratory Values, m/*n* (%)			
ALT≥ 3 × ULN, consecutive	31/10,341 (0.30)	50/11,512 (0.43)	0.084
AST≥ 3 × ULN, consecutive	23/10,342 (0.22)	30/11,512 (0.26)	0.525
ALT or AST≥ 3 × ULN, consecutive	36/10,342 (0.35)	64/11,512 (0.56)	**0.017**
CK≥ 10 × ULN	13/10,342 (0.13)	9/11,514 (0.08)	0.350
Myopathy†	4/10,342 (0.04)	3/11,512 (0.03)	0.67
Rhabdomyolysis‡	0/10,342 (0.00)	0/11,512 (0.00)	N/A
Specific AE groups, *n* (%)	**(*n* = 10,505)**	**(*n* = 11,705)**	
Hepatitis-related§	8 (0.08)	5 (0.04)	0.359
Gallbladder-related¶	10 (0.10)	14 (0.12)	0.522
Gastrointestinal-related**	792 (7.54)	832 (7.11)	0.112
Allergic reaction or rash††	139 (1.32)	185 (1.58)	0.254

Definitions of specific AE groups apply to all subgroup tables:

*Considered by the investigator to be possibly, probably or definitely related to study drug.

†Myopathy is defined as CK elevation > 10 × ULN with associated muscle symptoms with no other explanatory cause.

‡Rhabdomyolysis is defined as myopathy with associated evidence of renal damage.

§In addition to review of the effects of ezetimibe + statin on laboratory parameters associated with liver function, ''hepatitis-related'' clinical AE terms (preferred MedDRA terms) were pre-identified for collective review, and included cholestasis, hepatitis, hepatic lesion, hepatomegaly, hepatic cyst, hepatitis cholestatic.

¶For gallbladder-related clinical AEs the preferred terms (preferred MedDRA terms) were pre-identified for collective review, including bile duct obstruction, biliary colic, cholangitis, cholecystitis, cholecystitis chronic, cholelithiasis, and gallbladder disorder.

**For gastrointestinal-related clinical AEs, the preferred terms (preferred MedDRA terms) were pre-identified for collective review, and included abdominal discomfort, abdominal distension, abdominal pain, abdominal tenderness, colitis, colonic polyp, constipation, dental caries, dental discomfort, diarrhoea, diverticulum, duodenitis, dyspepsiea, dysphagia, erosive duodenitis, faeces discolored, flatulence, food poisoning, gastritis, gastroesophageal reflux disease, gingival pain, haemorrhoids, hiatus hernia, nausea, oesophageal stenosis, rectal haemorrhage, tooth loss, toothache,and vomiting.

††For allergic reaction or rash the preferred terms (preferred MedDRA terms) were pre-identified for collective review, and included analphylaxis, angioedema, dermatitis, dermagraphism, drug hypersensitivity, eczema, eosinophilia, erythema, face oedema, hypersensitivity, palmar erythema, periorbital oedema, photodermatosis, photosensitivity, pigmentation disorder, priuritus, rash, rosacea, skin disorder, skin exfoliation, skin hyperpigmentation, skin inflammation, skin lesion, subcutaneious nodule, systemic lupus erythematosus rash, and urticaria.

to the statin + ezetimibe combination groups within the studies included. A total of 22,278 patients received at least one dose of study drug and were included in the safety analysis (Table 1).

Baseline characteristics

Baseline characteristics were generally similar between treatment groups in the full cohort (Table 2). The majority of the intent-to-treat (ITT) population was Caucasian and the mean age (± standard deviation) was 60 ± 11 years with a mean body mass index (BMI) of 29.8 kg/m^2. Half of subjects (50.1%) had metabolic syndrome, and approximately 1/3 of subjects had CHD (34%) or diabetes mellitus (30%). At baseline, 57% of subjects were treated as first-line, and these subjects received statin monotherapy more often than receiving combination statin/ezetimibe (61% vs. 54%).

In the subgroups that were compared (Table 2), a smaller proportion of women had CHD compared

with men, and a greater proportion of women had metabolic syndrome compared with men. Compared with older subjects (≥ 65 years), younger subjects (< 65 years) had a higher proportion of non-Caucasians and a higher proportion of subjects that were treated with first-line therapy. The older group included a higher proportion of subjects with CHD, diabetes mellitus, and metabolic syndrome compared with the younger age group. Compared with the White and Other subgroups, Black subjects had a higher proportion of females and subjects treated with first-line therapy. Blacks had the lowest proportion of subjects with CHD, while Whites had the lowest proportion of subjects with diabetes mellitus and metabolic syndrome. When comparing first-line with second-line studies, subjects that were treated with second-line therapy tended to be older by approximately 4.5 years, and included a higher proportion of males, subjects with CHD, and subjects with diabetes mellitus, but included a smaller proportion of subjects with metabolic syndrome and non-Caucasians. Although *mean* BMI was similar between all subgroups, women, subjects ≥ 65 years, Black subjects and subjects treated first-line had higher proportions with BMI ≥ 30 kg/m^2.

Safety results

In the full cohort (Table 3), the only significant difference between treatments was in consecutive AST or ALT elevations ≥ 3 × ULN. Although the incidence (0.35% vs. 0.56%, statin vs. statin/ezetimibe) was small in both treatment groups, there were significantly more reports of elevations in subjects treated with ezetimibe/statin therapy (p = 0.017). Otherwise, both treatments had generally similar tolerability and safety profiles (i.e., there were no between-treatment differences in the proportion of subjects reporting ≥ 1 AEs, drug-related AEs, serious AEs, serious drug-related AEs, discontinuations due to AEs, or CK elevations ≥ 10 × ULN). There was no difference in the incidence of myopathy, which was small in both treatment groups (0.03%–0.04%), and there were no cases of rhabdomyolysis in any of the studies. A total of 12 deaths were reported during

Table 4 Summary of safety data in men and women

	Male		Female		p-value for effects		
	Statin	Statin/EZ	Statin	Statin/EZ	Treatment	Sex	Sex by treatment interaction
AE summary, *n* (%)	**(*n* = 5380)**	**(*n* = 6129)**	**(*n* = 5137)**	**(*n* = 5585)**			
≥ 1 AE	1537 (28.57)	1779 (29.03)	1918 (37.34)	1938 (34.70)	–	< 0.001	0.014
Drug-related* AE	349 (6.49)	456 (7.44)	484 (9.42)	505 (9.04)	0.017	< 0.001	–
Serious AEs (SAEs)	74 (1.38)	107 (1.75)	71 (1.38)	80 (1.43)	–	–	–
Drug-related* SAEs	2 (0.04)	8 (0.13)	4 (0.08)	5 (0.09)	–	–	–
Death	4 (0.07)	3 (0.05)	1 (0.02)	4 (0.07)	–	–	–
Discontinuations							
Due to an AE	91 (1.69)	105 (1.71)	128 (2.49)	158 (2.83)	–	0.016	–
Due to drug-related* AE	49 (0.91)	69 (1.13)	87 (1.69)	108 (1.93)	–	0.002	–
Due to SAEs	18 (0.33)	23 (0.38)	16 (0.31)	15 (0.27)	–	–	–
Due to drug-related* SAEs	2 (0.04)	4 (0.07)	4 (0.08)	3 (0.05)	–	–	–
Laboratory values, m/*n* (%)							
ALT≥ 3 × ULN, consecutive	15/5289 (0.28)	34/6031 (0.56)	16/5052 (0.32)	16/5481 (0.29)	0.018	–	–
AST≥ 3 × ULN, consecutive	7/5290 (0.13)	16/6031 (0.27)	16/5052 (0.32)	14/5481 (0.26)	–	0.049	–
ALT or AST≥ 3 × ULN, consecutive	17/5290 (0.32)	41/6031 (0.68)	19/5052 (0.38)	23/5481 (0.42)	0.005	–	–
CK≥ 10 × ULN	9/5290 (0.17)	7/6033 (0.12)	4/5052 (0.08)	2/5481 (0.04)	–	–	–
Myopathy	2/5290 (0.04)	2/6033 (0.03)	2/5052 (0.04)	1/5481 (0.02)	–	–	–
Rhabdomyolysis	0/5290 (0.00)	0/6033 (0.00)	0/5052 (0.00)	0/5481 (0.00)	–	–	–
Specific AE groups†, *n* (%)	**(*n* = 5372)**	**(*n* = 6124)**	**(*n* = 5133)**	**(*n* = 5581)**			
Hepatitis-related	4 (0.07)	4 (0.07)	4 (0.08)	1 (0.02)	–	–	–
Gallbladder-related	3 (0.06)	6 (0.10)	7 (0.14)	8 (0.14)	–	–	–
Gastrointestinal-related	324 (6.03)	370 (6.04)	468 (9.12)	462 (8.28)	–	< .001	–
Allergic reaction or rash	50 (0.93)	79 (1.29)	89 (1.73)	106 (1.90)	–	< .001	–

*Considered by the investigator to be possibly, probably or definitely related to study drug.
†Definitions of specific AE groups are the same as those in Table 3.

the course of all 27 studies and none of the deaths were attributed to treatment. The causes of the five deaths in the statin group were due to head injury after a fall, chronic obstructive pulmonary disease, sudden cardiac death, mixed drug ingestion, and myocardial infarction. The causes of the seven deaths in the statin/ezetimibe group were suicide, two deaths due to head injury, hypotension/respiratory failure, cardiac arrest, stroke, and spontaneous abortion leading to fetal death. The results of the sensitivity analysis were consistent with the original logistic regression model analysis, with statistically significantly greater reports in consecutive AST or ALT elevations $\geq 3 \times$ ULN in ezetimibe/statin-treated subjects compared with statin monotherapy-treated subjects ($p = 0.041$).

Generally, higher AE rates were reported for women regardless of treatment (Table 4). When comparing the sexes, women reported significantly more AEs (i.e., ≥ 1 AE), drug-related AEs, discontinuations due to AEs, discontinuations due to drug-related AEs, gastrointestinal-related AEs, allergic reaction- or rash-related AEs and AST elevations $\geq 3 \times$ ULN than men. Among men, a significantly greater proportion treated with the combination of statin/ezetimibe reported AST or ALT elevations $\geq 3 \times$ ULN, and ALT elevations $\geq 3 \times$ ULN than those treated with statin alone. There were no significant differences between men and women in the occurrence of myopathy, which was small in both sexes.

Generally similar rates of AEs were reported between the age groups (Table 5), although significantly more reports of drug-related serious AEs occurred in the statin/ezetimibe group and this was driven mainly by reports in subjects < 65 years. Also among subjects < 65 years of age, those being treated with the combination statin/ezetimibe reported significantly more discontinuations due to drug-related serious AEs, and ALT and/or AST elevations $\geq 3 \times$ ULN compared with subjects ≥ 65 years treated with statin alone. Significantly more subjects ≥ 65 years reported serious AEs and discontinued due to serious AEs compared with subjects < 65 years, whereas significantly more subjects

Table 5 Summary of safety data by age group

	< 65 years		≥ 65 years		p-value for effects		
	Statin	Statin/EZ	Statin	Statin/EZ	Treatment	Age	Age by treatment interaction
AE summary, *n* (%)	**(*n* = 6816)**	**(*n* = 7406)**	**(*n* = 3701)**	**(*n* = 4308)**			
≥ 1 AE	2368 (34.74)	2426 (32.76)	1087 (29.37)	1291 (29.97)	–	–	–
Drug-related* AE	577 (8.47)	638 (8.61)	256 (6.92)	323 (7.50)	–	–	–
Serious AEs (SAEs)	74 (1.09)	93 (1.26)	71 (1.92)	94 (2.18)	–	< 0.001	–
Drug-related* SAEs	3 (0.04)	13 (0.18)	3 (0.08)	0 (0.00)	0.014	–	0.003
Death	4 (0.06)	3 (0.04)	1 (0.03)	4 (0.09)	–	–	–
Discontinuations							
Due to an AE	137 (2.01)	160 (2.16)	82 (2.22)	103 (2.39)	–	–	–
Due to drug-related* AE	90 (1.32)	114 (1.54)	46 (1.24)	63 (1.46)	–	–	–
Due to SAEs	17 (0.25)	18 (0.24)	17 (0.46)	20 (0.46)	–	0.035	–
Due to drug-related* SAEs	3 (0.04)	7 (0.09)	3 (0.08)	0 (0.00)	–	–	0.014
Laboratory values, m/*n* (%)							
ALT≥ 3 × ULN, consecutive	21/6698 (0.31)	44/7270 (0.61)	10/3643 (0.27)	6/4242 (0.14)	0.009	–	0.020
AST≥ 3 × ULN, consecutive	12/6699 (0.18)	24/7270 (0.33)	11/3643 (0.30)	6/4242 (0.14)	–	–	0.023
ALT or AST≥ 3 × ULN, consecutive	23/6699 (0.34)	56/7270 (0.77)	13/3643 (0.36)	8/4242 (0.19)	0.001	–	0.004
CK≥ 10 × ULN	12/6699 (0.18)	7/7272 (0.10)	1/3643 (0.03)	2/4242 (0.05)	–	0.049	–
Myopathy	3/ 6699 (0.03)	2/7272 (0.02)	1/3643 (0.03)	1/4242 (0.02)	–	–	–
Rhabdomyolysis	0/ 6699 (0.00)	0/7272 (0.00)	0/3643 (0.00)	0/4242 (0.00)	–	–	–
Specific AE groups†, *n* (%)	**(*n* = 6809)**	**(*n* = 7401)**	**(*n* = 3696)**	**(*n* = 4304)**			
Hepatitis-related	6 (0.09)	3 (0.04)	2 (0.05)	2 (0.05)	–	–	–
Gallbladder-related	7 (0.10)	5 (0.07)	3 (0.08)	9 (0.21)	–	–	–
Gastrointestinal-related	543 (7.97)	542 (7.32)	249 (6.74)	290 (6.74)	–	–	–
Allergic reaction or rash	102 (1.50)	124 (1.68)	37 (1.00)	61 (1.42)	–	–	–

*Considered by the investigator to be possibly, probably or definitely related to study drug.
†Definitions of specific AE groups are the same as those in Table 3.

< 65 years reported CK elevations ≥ 10 × ULN compared with subjects ≥ 65 years. There were no significant differences between subjects < 65 years and ≥ 65 years in the occurrence of myopathy regardless of treatment, which was small in both age groups.

Likewise, there were generally similar rates of AEs reported between race subgroups (Table 6), with a few exceptions. Subjects in the 'Other' subgroup reported significantly fewer AEs (i.e., ≥ 1 AE) and drug-related AEs compared with Black or White subjects. Among White subjects, significantly more who were treated with the combinations of statin/ezetimibe experienced AST or ALT elevations ≥ 3 × ULN compared with White subjects treated with statin monotherapy, although the incidence was low. There was no other difference between treatments in the Black or Other subgroups. Finally, although the proportions were very small (< 1%) in both treatment groups in all three race subgroups overall, among Black subjects, there was a significantly higher proportion of CK elevations ≥ 10 × ULN treated with statin monotherapy compared with statin/ezetimibe combination (0.69% vs. 0.0%). There were no significant differences between race groups in the occurrence of myopathy, which was low in all three groups.

There was a significant effect of treatment, as well as a first-line/second-line by treatment interaction on serious AEs, with more reports in the combination of statin/ezetimibe vs. statin monotherapy in subjects who were taking ongoing statin at study entry (subjects treated second-line) (Table 7). There was also a significant effect of treatment on allergic reaction or rash AEs, with more reports in the combination of statin/ezetimibe vs. statin monotherapy in both first-line and subjects treated second-line (Table 7). A significantly greater proportion of subjects who were treated first-line reported ≥ 1 AE, drug-related AEs, serious AEs, potentially hepatitis-related AEs, gastrointestinal-related AEs, allergic

Table 6 Summary of safety data by race groups

	White		Black		Other		p-value for effects		
	Statin	Statin/EZ	Statin	Statin/EZ	Statin	Statin/EZ	Treatment	Race	Race by treatment interaction
AE summary, *n* (%)	**(*n* = 8837)**	**(*n* = 9888)**	**(*n* = 738)**	**(*n* = 830)**	**(*n* = 942)**	**(*n* = 996)**			
≥ 1 AE	2911 (32.94)	3170 (32.06)	256 (34.69)	279 (33.61)	288 (30.57)	268 (26.91)	–	0.048	–
Drug-related* AE	714 (8.08)	821 (8.30)	65 (8.81)	72 (8.67)	54 (5.73)	68 (6.83)	–	0.037	–
Serious AEs (SAEs)	127 (1.44)	165 (1.67)	10 (1.36)	12 (1.45)	8 (0.85)	10 (1.00)	–	–	–
Drug-related* SAEs	5 (0.06)	9 (0.09)	1 (0.14)	1 (0.12)	0 (0.00)	3 (0.30)	–	–	–
Death	5 (0.06)	6 (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.10)	–	–	–
Discontinuations								–	–
Due to an AE	188 (2.13)	232 (2.35)	16 (2.17)	13 (1.57)	15 (1.59)	18 (1.81)	–	–	–
Due to drug-related* AE	118 (1.34)	158 (1.60)	9 (1.22)	7 (0.84)	9 (0.96)	12 (1.20)	–	–	–
Due to SAEs	30 (0.34)	30 (0.30)	3 (0.41)	3 (0.36)	1 (0.11)	5 (0.50)	–	–	–
Due to drug-related* SAEs	5 (0.06)	4 (0.04)	1 (0.14)	0 (0.00)	0 (0.00)	3 (0.30)	–	–	–
Laboratory values, m/*n* (%)									
ALT≥ 3 × ULN, consecutive	24/8701 (0.28)	41/9726 (0.42)	2/727 (0.28)	3/810 (0.37)	5/913 (0.55)	6/976 (0.61)	–	–	–
AST≥ 3 × ULN, consecutive	20/8702 (0.23)	24/9726 (0.25)	0/727 (0.00)	0/810 (0.00)	3/913 (0.33)	6/976 (0.61)	–	0.004	–
ALT or AST≥ 3 × ULN, consecutive	29/8702 (0.33)	53/9726 (0.54)	2/727 (0.28)	3/810 (0.37)	5/913 (0.55)	8/976 (0.82)	0.024	–	–
CK≥ 10 × ULN	7/8702 (0.08)	6/9728 (0.06)	5/727 (0.69)	0/810 (0.00)	1/913 (0.11)	3/976 (0.31)	–	0.008	0.023
Myopathy	2/8702 (0.02)	1/9728 (0.01)	1/727 (0.14)	1/810 (0.12)	1/913 (0.11)	1/976 (0.10)	–	–	–
Rhabdomyolysis	0/8702 (0.00)	0/9728 (0.00)	0/727 (0.00)	0/810 (0.00)	0/913 (0.00)	3/976 (0.31)	–	–	–
Specific AE groups†, *n* (%)	**(*n* = 8842)**	**(*n* = 9893)**	**(*n* = 737)**	**(*n* = 828)**	**(*n* = 926)**	**(*n* = 983)**			
Hepatitis-related	8 (0.09)	4 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.10)	–	–	–
Gallbladder-related	10 (0.11)	13 (0.13)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.10)	–	–	–
Gastrointestinal-related	675 (7.63)	720 (7.28)	48 (6.51)	59 (7.13)	69 (7.45)	53 (5.39)	–	–	–
Allergic reaction or rash	114 (1.29)	160 (1.62)	8 (1.09)	14 (1.69)	17 (1.84)	11 (1.12)	–	–	–

*Considered by the investigator to be possibly, probably or definitely related to study drug.
†Definitions of specific AE groups are the same as those in Table 3.

Table 7. Summary of safety data in patients grouped by those receiving first-line treatment or second-line treatment

	First-line		Second-line		p-value for effects		
	Statin	Statin/EZ	Statin	Statin/EZ	Treatment	First/second line	First-/second-line by treatment interaction
AE summary, *n* (%)	**(*n* = 6694)**	**(*n* = 6664)**	**(*n* = 3823)**	**(*n* = 5050)**			
≥ 1 AE	2553 (38.14)	2510 (37.67)	902 (23.59)	1207 (29.90)	–	< 0.001	–
Drug-related* AE	591 (8.83)	636 (9.54)	242 (6.33)	325 (6.44)	–	< 0.001	–
Serious AEs (SAEs)	95 (1.42)	91 (1.37)	50 (1.31)	96 (1.90)	0.016	–	0.035
Drug-related* SAEs	4 (0.06)	9 (0.14)	2 (0.05)	4 (0.08)	–	–	–
Death	4 (0.06)	3 (0.04)	2 (0.05)	3 (0.06)	–	–	–
Discontinuations							
Due to an AE	150 (2.24)	170 (2.55)	69 (1.80)	93 (1.84)	–	–	–
Due to drug-related* AE	91 (1.36)	116 (1.74)	45 (1.18)	61 (1.21)	–	–	–
Due to SAEs	25 (0.37)	25 (0.38)	9 (0.24)	13 (0.26)	–	–	–
Due to drug-related* SAEs	4 (0.06)	6 (0.09)	2 (0.05)	1 (0.02)	–	–	–
Laboratory values, m/*n* (%)							
ALT≥ 3 × ULN, consecutive	22/6586 (0.33)	32/6557 (0.49)	9/3755 (0.24)	18/4955 (0.36)	–	–	–
AST≥ 3 × ULN, consecutive	18/6587 (0.27)	17/6557 (0.26)	5/3755 (0.13)	13/4955 (0.26)	–	–	–
ALT or AST≥ 3 × ULN, consecutive	26/6587 (0.39)	41/6557 (0.63)	10/3755 (0.27)	23/4955 (0.46)	–	–	–
CK≥ 10 × ULN	12/6587 (0.18)	7/6558 (0.11)	1/3755 (0.03)	2/4956 (0.04)	–	0.016	–
Myopathy	3/6587 (0.05)	3/6558 (0.05)	1/3755 (0.03)	0/4956 (0.00)	–	–	–
Rhabdomyolysis	0/6587 (0.00)	0/6558 (0.00)	0/3755 (0.00)	N/A	–	–	–
Specific AE groups†, *n* (%)	**(*n* = 6684)**	**(*n* = 6662)**	**(*n* = 3821)**	**(*n* = 5043)**			
Hepatitis-related	8 (0.12)	5 (0.08)	0 (0.00)	0 (0.00)	–	< 0.001	–
Gallbladder-related	8 (0.12)	7 (0.11)	2 (0.05)	7 (0.14)	–	–	–
Gastrointestinal-related	618 (9.25)	572 (8.59)	174 (4.55)	260 (5.16)	–	< 0.001	0.010
Allergic reaction or rash	122 (1.83)	140 (2.10)	17 (0.44)	45 (0.89)	0.030	< 0.001	0.044

*Considered by the investigator to be possibly, probably or definitely related to study drug.
†Definitions of specific AE groups are the same as those in Table 3.

reaction or rash AEs, and CK elevations ≥ 10 × ULN compared with subjects treated second-line in both treatment groups (Table 7). There was no significant difference between subjects treated first-line compared with second-line in the occurrence of myopathy, which was low overall.

Discussion

The efficacy and safety profiles of ezetimibe, statins, and the combination of ezetimibe with various doses of statins have been well-established by numerous clinical trials in the general population. The accumulation of study data into a large database from 27 studies conducted over several years provided the opportunity to assess the safety and tolerability profiles of ezetimibe combined with statins in the overall population and in population subgroups with increased statistical power. The results of this pooled analysis confirm that the overall safety and tolerability profiles of ezetimibe added to a statin are generally comparable to statin monotherapy for up to 24 weeks. Irrespective of treatment group, generally higher rates of AEs were reported in women compared with men, and generally similar rates of AEs were reported between races and between age groups. More AEs were reported by subjects in first-line studies than subjects in second-line studies. The occurrence of myopathy was low and did not differ between treatments or any of the subgroups studied.

Although the incidence was low, elevations in liver enzymes were observed more often with ezetimibe/statin combination treatment compared with statin monotherapy in the overall population and in most subgroups studied. These rates were consistent with the incidence reported in the prescribing information for statin monotherapy (0.7%–1.9%) and ezetimibe combined with simvastatin (Vytorin; 1.7%) (13,14) Similarly, in an efficacy and safety analysis conducted in the same database as this

pooled analysis, but in both subgroups of patients with and without diabetes, consecutive or presumed consecutive elevations > 3 × ULN in liver enzymes were also noted somewhat more frequently in subjects receiving ezetimibe/statin combination compared with statin monotherapy (12).

There was a statistically significant treatment effect reported for CK elevations ≥ 10 × ULN among Black subjects, with increases observed significantly more often with statin monotherapy vs. the combination treatment. However, these elevations resulted in myopathy in only two cases, one in each treatment group. Given the small number of events, this was likely a chance imbalance. No such racial imbalances in the incidence of myopathy have been identified in the literature. Additional safety studies with an even greater number of Black subjects and prespecified endpoints are needed to produce conclusive evidence about muscle-related safety with statin and/or ezetimibe-plus-statin treatment.

Interestingly, although there was no treatment effect among subjects grouped by age, there was an age effect with more subjects in the younger age group reporting CK elevations ≥ 10 × ULN compared with older subjects. Based on what is known about the increased risk of myopathy, (which involves CK elevations) in older subjects, one would predict that more subjects in the older age group would have CK elevations ≥ 10 × ULN compared with younger subjects (5,15). One explanation may be that there was a much higher proportion of subjects < 65 years included in the first-line studies compared with second-line studies, which also reported a significantly greater effect on CK elevations ≥ 10 × ULN, and therefore many older subjects included in this pooled analysis may have been screened out for adverse effects or risk for CK elevations. Indeed, screening out for tolerability issues may explain why subjects treated second-line reported significantly fewer clinical and laboratory AEs compared with subjects treated first-line. In the second-line studies, subjects who experienced AEs most likely did not continue to randomization.

There were some differences between the sexes, with women reporting significantly more clinical AEs and discontinued treatment due to AEs compared with men, regardless of treatment. In addition to potential tolerability issues in women, liver enzyme elevations were more common with the combination treatment than with statin monotherapy in men, but not in women. More than 40% of the men included in these trials were diagnosed with CHD at baseline compared with 26% among women. It is possible that men were taking more concomitant medications, which affected drug metabolism and contributed to elevations in liver enzymes. An evaluation of ALT and CK elevation in an ambulatory care setting ($N = 4958$) found that significant elevations in either ALT or CK during ezetimibe treatment is usually associated with concomitant medications and that rates of ALT and/or CK elevations were similar to that of placebo (16).

Limitations

These trials were short-term (6–24 weeks, mean duration of follow-up = 9 weeks), and therefore could not assess long-term safety and tolerability. However, long-term trials have also documented the safety of ezetimibe combined with statin therapy (17–20). In addition, many patients had been receiving statins prior to enrolling in the trials, and this likely would influence the on-study AE profile. Further studies assessing tolerability in patients without previous statin treatment may help clarify whether specific subgroups are more likely to experience particular AEs. Although rosuvastatin was assessed as a monotherapy, there were no treatment arms that included the combination of ezetimibe with rosuvastatin included in this database. However, clinical experience suggests that the safety and tolerability profiles of that combination would be generally similar to other statin/ezetimibe combinations (21–23).

Conclusion

In conclusion, ezetimibe added to a statin and statin monotherapy both provide generally safe and well-tolerated therapeutic options for dyslipidemia. These results describe the safety profiles over 6–24 weeks of widely used lipid-lowering therapies and encourage appropriate and judicious use of lipid-altering therapy in certain subpopulations. Individual monitoring in patients with risk factors, such as older females or those taking concomitant medications is warranted. Finally, the results of this analysis confirm the results of a previous systematic review concluding that the addition of ezetimibe to a statin appears unlikely to increase the incidence of myopathy (6).

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