Efficacy and safety of fluvastatin ER 80 mg compared with fluvastatin IR 40 mg in the treatment of primary hypercholesterolaemia

WILLIAM INSULL JR, ADRIAN D MARAIS, RONNIE ARONSON, SHERYL MANFREDA, AND THE FLUVASTATIN STUDY GROUP

Abstract

The efficacy and safety of once- or twice-daily immediate-release (IR) fluvastatin 40 mg were compared with those of the extended-release (XL) formulation of fluvastatin 80 mg every night (qpm), which facilitates sustained drug delivery. Patients (n=442) with primary hypercholesterolaemia (Fredrickson types IIa and IIb) were randomised to the three treatment groups in the ratio 1:1:1. Active treatment was administered for 24 weeks, following a four-week placebo/dietary lead-in period.

At week 24, the mean reduction in low density lipoprotein cholesterol levels in patients treated with fluvastatin XL 80 mg every night (qpm) (-33.5%) was significantly greater than in the fluvastatin IR 40 mg every night (qpm) group (-23.2%; p<0.001), and similar to the reduction for patients treated with fluvastatin IR 40 mg twice-daily (bid) (-31.4%). Significant and dose-related alterations in other lipid variables were also apparent, particularly for high density lipoprotein cholesterol (10.2% increase) and apolipoprotein A1 and B levels (+11.5% and -24.2%, respectively) in the fluvastatin XL 80 mg qpm group compared with the fluvastatin IR 40 mg qpm group (all p<0.001). Mean triglyceride levels decreased by 14.6% in the fluvastatin XL 80 mg qpm group. Adverse events were generally mild, with no differences in frequency across the groups. Fluvastatin XL 80 mg qpm is a safe and effective lipid-lowering treatment for patients with type II hypercholesterolaemia.

Baylor College of Medicine, The Methodist Hospital, 6560 Fannin Street #1150, Houston, TX 77030, USA.
William Insull Jr, Director, Lipid Research Clinic

Cape Heart Centre and MRC Cape Heart Group, University of Cape Town Health Sciences Faculty, Observatory, South Africa.
Adrian D Marais, Associate Professor

Lifestyle Metabolism Center, Toronto, Ontario, Canada.
Ronnie Aronson, Director

Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.
Sheryl Manfreda, Associate Director, Clinical Research

Correspondence to: Dr W Insull
(email: winsull@bcm.tmc.edu)

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Introduction

Atherosclerosis of the coronary and peripheral vasculature is the leading cause of death among men and women worldwide.[1] There is now considerable evidence that controlling hypercholesterolaemia can reduce the incidence of coronary heart disease.[2] Whilst the main focus of treatment has been directed at lowering levels of low density lipoprotein cholesterol (LDL-C), other lipid variables are also important. Patients rarely present with elevated LDL-C in isolation, and low levels of high density lipoprotein cholesterol (HDL-C) are often the predominant lipid abnormality among patients with coronary artery disease.[3] An increase in HDL-C level of as little as 6%, accompanied by triglyceride (TG) reductions of 31%, has been associated with a 22% reduction in cardiovascular events.[4]

Elevated TG levels are a significant coronary risk factor, particularly in women; levels are also increased in older patients.[5] Apolipoproteins A1 and B (apo A1 and apo B) comprise the two major proteins associated with HDL-C and LDL-C, respectively. Levels of apo A1 are inversely related to the incidence of coronary heart disease, whereas apo B levels are correlated directly with an increased risk of disease.[6] Statins have been shown to reduce the incidence of coronary heart disease significantly and can reduce the risk of death by 30%.[7-11]

Fluvastatin is a synthetic competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. It is an effective and well-tolerated treatment for primary hypercholesterolaemia, associated with mean reductions in LDL-C of up to 36% during long-term treatment.[12] Fluvastatin is also associated with significant reductions in apo B levels, LDL:HDL ratio, and very low density lipoprotein cholesterol (VLDL-C) and TGs, and with increases in HDL-C.[12] The benefit of fluvastatin is reflected in the concomitant reduction in frequency of coronary events, including cardiac death, angina pectoris and myocardial infarction.[13,14]

The pharmacokinetics of fluvastatin IR are non-linear, particularly at high doses.[15,16] Delivering the active drug to the liver in a sustained but slower fashion would be expected to provide greater hepatic availability, without elevating systemic drug levels or compromising safety profiles. Additionally, a once-daily

dosage would be likely to increase patient compliance. A new once-daily formulation of fluvastatin (80 mg matrix tablet) that releases the drug steadily over eight hours has therefore been developed (Novartis Pharma, Basel, Switzerland). Fluvastatin is incorporated into a hydrophilic cellulose matrix that swells when in contact with fluid in the intestine; the drug is released by diffusion over eight hours. This new extended-release (XL) formulation achieves mean LDL-C reductions in the range of 35% and mean HDL-C elevations of up to 9%.[17]

This study was conducted to assess the efficacy and safety of the XL 80 mg formulation of fluvastatin, compared with fluvastatin IR 40 mg given twice a day (bid) or once-daily at night (qpm), to patients with primary hypercholesterolaemia with or without moderate hypertriglyceridaemia (Fredrickson types IIa or IIb).

Methods

Study design

A prospective, double-blind, parallel-group, study was carried out in 29 centres in six countries (USA, Canada, Turkey, New Zealand, Australia and South Africa). The study was performed in accordance with the Declaration of Helsinki and its subsequent amendments. Local ethics committees approved the study protocol, and all patients gave written informed consent. The primary efficacy variable was the percentage change from baseline in LDL-C. Secondary efficacy variables were percentage changes from baseline in total cholesterol (TC), HDL-C, TG, LDL:HDL ratio, apo A1 and apo B.

Adverse events were also recorded. The relationship between these and study medication was assessed by each principal investigator using the following criteria, which were included in this study protocol: i) Not suspected (the temporal relationship of the clinical event to study drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event); ii) suspected (the temporal relationship of the clinical event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event).

As the patients were relatively healthy, musculoskeletal pain was reported as related to acute physical situations (i.e. gardening, physical sporting activities, etc.) in the majority of cases.

Patients

Patients were aged ≥ 18 years with primary hypercholesterolaemia (Fredrickson types IIa or IIb), elevated LDL-C level (≥ 4.1 mmol/L [≥ 160 mg/dl]) and plasma TG level (≤ 4.5 mmol/L [≤ 400 mg/dl]) at each of two visits during the dietary lead-in period. All patients started a low saturated-fat and low-cholesterol diet at least four weeks before the lead-in period (European Atherosclerosis Society [EAS] or National Cholesterol Education Program [NCEP] Step I or II). All female patients of childbearing potential were non-pregnant, non-lactating and using approved physical methods of contraception.

The principal exclusion criteria were homozygous familial hypercholesterolaemia and type I, III, IV, V or secondary hyperlipoproteinaemia. Additionally, patients with the following conditions were ineligible: evidence of liver or renal impairment; diabetes mellitus; surgical or medical conditions likely to alter significantly the absorption, distribution, metabolism or excretion of any drug; congestive heart failure (unless stable and clinically controlled); severe or unstable angina; myocardial infarction; major surgery or angioplasty during the six months prior to the beginning of the dietary lead-in period; poorly controlled or uncontrolled hypertension; prior or current muscle disease of any type; or a history of resistance to lipid-lowering agents. Patients had neither received other lipid-lowering agents within four weeks of the first lipid determination nor taken probucol during the previous year.

Following the four-week dietary lead-in period, and fulfilment of the entry criteria, 442 patients were randomised (balanced 1:1:1) among the following three treatment groups: fluvastatin XL 80 mg qpm (at bedtime), fluvastatin IR 40 mg qpm (at bedtime) or fluvastatin IR 40 mg bid (at bedtime and before or with breakfast). The dosage forms (tablets for fluvastatin XL or capsules for fluvastatin IR) required the use of double-dummy blinding procedures.

Assessments

Patients were assessed at the beginning of the dietary/placebo period and two weeks later (weeks -4 and -2), at the start of the active treatment period (week 0), at weeks 2 and 4, and every four weeks for the following 24 weeks. An optional visit could be scheduled at week -1 to fulfil the lipid and biochemical entry criteria.

At each visit, after the patient had been sitting for at least three minutes, 12-hour fasting blood samples were obtained for determinations of TC, LDL-C, HDL-C, TG and LDL:HDL ratio. Apo A1 and apo B were evaluated at weeks 0, 12 and 24. LDL-C levels were calculated according to the formula of Friedewald (if TG levels were ≤ 4.5 mmol/L [≤ 400 mg/dl]); otherwise a direct analysis of LDL-C was performed (using an ultracentrifugation method) during the active treatment period for TG levels (> 4.5 mmol/L [> 400 mg/dl]).[18] All investigators, their staff and the patients remained blind to lipid levels throughout the study.

Blood pressure, heart rate, and liver and muscle enzymes were measured on each visit; measurement of body weight, haematological variables, urinalysis, blood chemistry analyses and physical examination were carried out at weeks -4, 0, 12 and 24. Electrocardiograms (ECGs) were taken and assessed at the beginning of the lead-in period and at the end of the study (weeks -4 and 24). Safety was assessed by continuously evaluating newly occurring and worsening adverse events and serious adverse events, as well as biochemical and ECG abnormalities, and the frequency of alanine aminotransferase/aspartate aminotransferase (ALT/AST) and creatine kinase (CK) elevations. The rate of patient withdrawal from the study due to adverse events or biochemical/haematological abnormalities was also monitored. All laboratory-based assays were performed by the Medical Research Laboratory (Highland Heights, Kentucky, USA)

Table 1. Summary of patient demographic and clinical characteristics at baseline for all randomised patients

Parameter	Fluvastatin XL 80 mg qpm (n=141)	Fluvastatin IR 40 mg qpm (n=146)	Fluvastatin IR 40 mg bid (n=155)
Mean age ± SD, years (range)	56.2±11.9 (22–77)	56.0±12.6 (20–83)	55.7±10.6 (27–82)
Age ≥ 65 years (%)	29.1%	25.3%	21.3%
Sex (male:female)	57:84	68:78	78:77
Race: Caucasian	113	133	134
Black	9	3	2
Other	19	10	19
Mean body mass index ± SD (kg/m^2)[a]	27.1±3.7	26.4±3.5	26.8±3.2
History of coronary heart disease, n (%)	46 (32.6)	52 (35.6)	50 (32.3)
Prior treatment with HMG-CoA reductase inhibitors, n (%)	77 (54.6)	66 (45.2)	82 (52.9)
Mean lipid values ± SD[b]:	n=139	n=143	n=152
LDL-C (mmol/L)	5.2±1.0	5.0±0.9	5.0±1.0
TC (mmol/L)	7.4±1.0	7.2±0.9	7.3±1.1
HDL-C (mmol/L)	1.3±0.3	1.4±0.3	1.3±0.3
TG (mmol/L)	2.0±0.8	1.9±0.7	2.1±0.8
LDL:HDL ratio	4.1±1.2	3.9±1.3	4.1±1.1
Apo A1 (g/L)[c]	1.5±0.3	1.5±0.2	1.5±0.3
Apo B (g/L)[d]	1.8±0.3	1.8±0.3	1.8±0.3

Key: XL = extended release; IR = immediate release; n = number of patients; SD = standard deviation; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; LDL = low density lipoprotein; HDL = high density lipoprotein; Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; qpm = every night; bid = twice-daily

[a] n=140, 146 and 153 for fluvastatin XL 80 mg qpm, fluvastatin IR 40 mg qpm and fluvastatin IR 40 mg bid, respectively.
[b] Categories include only patients in the intention-to-treat-analysis (n=139, 143 and 152 for the fluvastatin 80 mg qpm, fluvastatin IR 40 mg qpm and fluvastatin IR 40 mg bid groups, respectively).
[c] For apo A1, n=137 for fluvastatin XL 80 mg qpm and n=136 for fluvastatin IR 40 mg qpm or bid.
[d] For apo B, n=137 for fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid, and n=136 for fluvastatin IR 40 mg qpm.

or its affiliate Central Research Laboratories Europe (Zaventem, Belgium).

Statistical analysis

The target sample size was calculated to enable statistically valid comparison of treatment effects with respect to the percentage reduction in LDL-C for fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid, and was adjusted to ensure an adequate number of patients for the tolerability evaluation of fluvastatin XL. In particular, the target sample size was based on the null hypothesis that the treatment effect of fluvastatin XL 80 mg qpm, with respect to the percentage reduction from baseline in LDL-C, would be at least 5% less than that of fluvastatin IR 40 mg bid, versus the alternative hypothesis that the corresponding treatment effect of fluvastatin XL 80 mg qpm would not be less than that of fluvastatin IR 40 mg bid by 5% or more.

A sample size of 324 completed patients (108 patients per treatment group) was calculated as necessary to reject the null hypothesis with at least 90% power under the alternative hypothesis that the difference in mean percentage reduction from baseline in LDL-C between the two treatment groups would be zero, using a one-sided 2.5% significance level and assuming a standard deviation of approximately 11%, a reasonable estimate based on experience from previous similar fluvastatin trials.

Efficacy analyses were based on the intention-to-treat principle; namely, all randomised patients with a baseline and at least one post-baseline efficacy measurement for a given variable were included. A two-way analysis of variance (ANOVA) with treatment and centre as factors was used to compare least-squares mean percentage change from baseline in lipid variables between treatment groups. Changes were analysed from baseline to week 24 and at last assessment (last value carried forward). Baseline was defined as the mean value at week 0 and the value at the immediately preceding visit for all lipid variables except apo A1 and apo B, for which the week 0 values alone were taken as baseline. This enabled a more reliable baseline to be obtained as patient variability for LDL-C was taken into consideration. Week 0 values were used as the baseline for apo A1 and apo B. For the primary efficacy variable (LDL-C), tests for the comparability of fluvastatin XL 80 mg qpm and fluvastatin IR 40

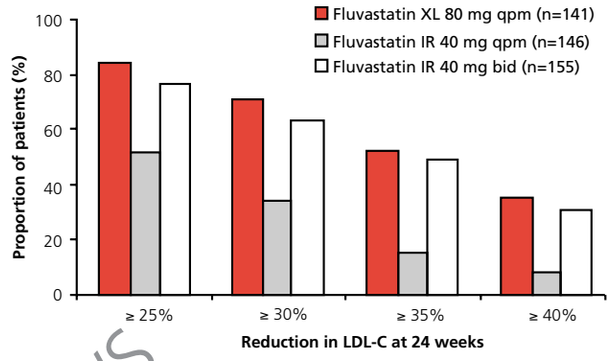
Table 2. Least-squares means (SE) for per cent change in lipid parameters from baseline to week 24 for all randomised patients

Parameter	Fluvastatin XL 80 mg qpm (n=125)	Fluvastatin IR 40 mg qpm (n=125)	Fluvastatin IR 40 mg bid (n=120)
LDL-C	-33.5 (1.30)***	-23.2 (1.26)	-31.4 (1.30)
HDL-C	10.2 (1.13)***	5.0 (1.10)	7.9 (1.14)
LDL:HDL ratio	-39.0 (1.36)*** *	-26.3 (1.33)	-35.7 (1.37)
TC	-23.7 (1.00)***	-16.5 (0.97)	-22.4 (1.00)
TG	-14.6 (2.76)	-10.7 (2.68)	-14.3 (2.78)
Apo A1[a]	11.5 (1.12)***	6.9 (1.10)	9.5 (1.13)
Apo B[a]	-24.2 (1.31)***	-16.3 (1.29)	-22.9 (1.33)

Key: SE = standard error of the least-squares mean; XL = extended release; IR = immediate release; n = number of patients; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; TC = total cholesterol; TG = triglycerides; Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B

[a] For apo A1 and apo B, n=123 and n=118 for fluvastatin IR 40 mg qpm and fluvastatin IR 40 mg bid, respectively.
***p<0.001 compared with fluvastatin 40 mg IR qpm (two-way ANOVA with treatment and centre as factors)
*p=0.05 compared with fluvastatin 40 mg IR bid (two-way ANOVA with treatment and centre as factors)

Figure 1. Patients achieving 25%, 30%, 35% and 40% reductions in low density lipoprotein cholesterol (LDL-C) according to treatment group after 24 weeks' treatment



Key: XL = extended release; IR = immediate release

mg bid were based on the following null hypothesis and one-sided alternative hypothesis:

$$H_0: \mu_{XL} < \mu_{IR\ bid} - 5\% \quad \text{versus} \quad H_a: \mu_{XL} > \mu_{IR\ bid} - 5\%$$

(where μ_{XL} and $\mu_{IR\ bid}$ are mean percentage reduction from baseline in LDL-C for fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid respectively).

Tests for the superiority of fluvastatin XL 80 mg qpm versus fluvastatin 40 mg qpm were based on the following null hypothesis and two-sided alternative hypothesis:

$$H_0: \mu_{XL} = \mu_{IR\ qpm} \quad \text{versus} \quad H_a: \mu_{XL} \neq \mu_{IR\ qpm}$$

(where μ_{XL} and $\mu_{IR\ qpm}$ are mean percentage reduction from baseline in LDL-C for fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg qpm respectively).

An overall two-sided significance level of 5% was preserved using Hochberg's multiple-testing step-up procedure.[19] For week 24 analyses of all lipid variables, two-sided 95% confidence intervals (CI) were calculated for between-treatment differences for all efficacy variables.

Results

A total of 442 patients were randomised to enter the trial. Of these, 371 patients (83.9%) completed 24 weeks of active treatment (126, 125 and 120 for fluvastatin XL 80 mg qpm, fluvastatin IR 40 mg qpm and fluvastatin IR 40 mg bid, respectively). The three treatment groups were similar in terms of baseline demographic and background characteristics (table 1). Baseline biochemical and haematological assessments were also similar across all treatment groups.

Efficacy analysis

Efficacy analysis at last assessment showed a significant 10.1% (95% CI: -13.5 to -6.7) greater decrease in LDL-C with fluvastatin XL 80 mg qpm versus fluvastatin IR 40 mg qpm (33.3% *vs.* 23.2% least-squares mean reductions in LDL-C from baseline, respectively) (p<0.001). The least-squares mean LDL-C reductions for the fluvastatin XL 80 qpm and fluvastatin IR 40 mg bid groups (33.3% and 30.7%, respectively) differed by 2.5% (95% CI: -5.9 to 0.9, p<0.001 for non-inferiority), indicating that the 80 mg XL form is at least therapeutically equivalent to fluvastatin 40 mg bid. Similar results were obtained at week 24, with a 10.3% (95% CI: -13.5 to -7.2) and a 2.2% (95% CI: -5.3 to 1.0) difference between fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg qpm and between fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid, respectively (table 2).

Median reductions in LDL-C at end point were 35%, 25% and 33% in the fluvastatin XL 80 mg qpm, IR 40 mg qpm and IR 40 mg bid groups, respectively. Most of the efficacy in reducing LDL-C was observed after two weeks, reaching the full effect after four weeks (-38.2%). This effect was maintained for the duration of the 24-week treatment period. At week 24, reductions ≥ 35% were achieved in approximately half of the patients treated with fluvastatin XL 80 mg qpm or fluvastatin IR 40 mg bid (51.2% and 47.5%, respectively; figure 1). Reductions ≥ 40% occurred in 33.6% of patients receiving fluvastatin XL 80 mg qpm and in 29.2% of patients receiving fluvastatin IR 40 mg bid. LDL-C reductions ≥ 25% were achieved in 51.2% of patients receiving fluvastatin IR 40 mg qpm.

Table 3. Mean (SD) and median per cent change from baseline to last assessment in lipid parameters, analysed according to phenotype: Fredrickson type IIa (TG level < 2.3 mmol/L [< 200 mg/dl]) or IIb (TG level ≥ 2.3 mmol/L [≥ 200 mg/dl])

Parameter	Fluvastatin XL 80 mg qpm		Fluvastatin IR 40 mg qpm		Fluvastatin IR 40 mg bid	
	IIa (n=95)	IIb(n=44)	IIa (n=106)	IIb (n=37)	IIa (n=97)	IIb (n=55)
LDL-C	-34.3 (14.4), -37	-30.2 (12.7), -30	-24.0 (12.7), -25	-20.8 (16.4), -23	-30.8 (14.8), -33	-30.1 (17.6), -33
HDL-C	7.8 (10.7), 8	13.5 (11.9), 14	3.8 (10.6), 4	3.3 (12.6), 4	5.7 (11.0), 5	7.4 (11.4), 6
TG	-11.2 (29.1), -17	-20.1 (21.2), -20	-8.0 (23.9), -8	-15.3 (26.5), -15	-9.2 (29.9), -16	-19.8 (25.7), -22

Key: SD = standard deviation; XL = extended release; IR = immediate release; n = number of patients; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; qpm = every night; bid = twice-daily

The effects of fluvastatin on other lipid variables are summarised in table 2. Mean HDL-C values were increased at week 24 in all treatment groups, with significantly greater improvements in the fluvastatin XL 80 mg qpm group (10.2%) compared with the fluvastatin IR 40 mg qpm group (5.0%; p<0.001).

The LDL:HDL ratio (3.9–4.1 at baseline) was reduced to the greatest extent in the fluvastatin XL 80 mg qpm group. Thus, for the fluvastatin XL 80 mg qpm group, the least-squares mean reduction at week 24 was 39.0% compared with 26.3% with fluvastatin IR 40 mg qpm (p<0.001) and 35.7% with fluvastatin IR 40 mg bid (p=0.05). Fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid were associated with equivalent reductions in TC, and these were significantly greater than those associated with fluvastatin IR 40 mg qpm (p<0.001 versus the fluvastatin XL 80 mg qpm group).

TG levels followed a similar pattern: clinically relevant reductions were achieved from baseline, but statistical tests were only performed between the treatment groups, and the between-group differences were not significant. Changes from baseline in apo A1 (increase) and apo B (decrease) were evident in all groups, with a significantly greater difference in the fluvastatin XL 80 mg qpm group compared with the fluvastatin IR 40 mg qpm group (p<0.001).

The mean reduction in TG was greater for patients with mixed dyslipidaemia (type IIb, baseline TG ≥ 2.3 mmol/L [≥ 200 mg/dl]) compared with patients exhibiting hypercholesterolaemia (type IIa; baseline TG < 2.3 mmol/L [< 200 mg/dl]) (table 3). Median decreases in TG levels for patients with type IIb dyslipidaemia were 20–22% in the fluvastatin XL 80 mg qpm and fluvastatin IR 40 mg bid groups, and 15% in the fluvastatin IR 40 mg qpm group. In addition, greater increases in HDL-C occurred in patients with mixed dyslipidaemia. Such patients often present with low baseline HDL-C levels (mean value of 1.2 mmol/L [46 mg/dl] for patients with mixed dyslipidaemia versus 1.4 mmol/L [55 mg/dl] for patients with type IIa hypercholesterolaemia in this study); there was a median increase of 14% in the fluvastatin XL 80 mg qpm group compared with median increases of 4% and 6% in the fluvastatin IR 40 mg qpm and bid groups, respectively (table 3). The study was not powered to determine the level of statistical significance of the differences between these patient groups.

Safety

A total of 437 patients were included in the safety analysis (fluvastatin XL 80 mg qpm n=139, fluvastatin IR 40 mg qpm n=145, fluvastatin IR 40 mg bid n=153). All patients received at least one dose of study medication and at least one post-baseline evaluation. No follow-up data were available from five randomised patients who were, therefore, not included in any of the safety assessments. Safety and tolerability were based on the evaluation of newly occurring and worsening (treatment-emergent) adverse events. Overall, the frequency of such events, most of which were mild or moderate, was similar across the three treatment groups (table 4). The proportion of adverse events suspected to be drug-related was generally low; the highest frequency of a specific suspected study-related adverse event was dyspepsia (5.2%), reported in the fluvastatin IR 40 mg bid group.

Twenty-five patients were withdrawn from the study due to adverse events during active treatment; 14 of these patients were withdrawn due to suspected drug-related events (five, five and four patients in the fluvastatin XL 80 mg qpm, fluvastatin 40 mg qpm and 40 mg bid groups, respectively). Three patients withdrew due to serious adverse events but none was related to the study drug, based on the criteria described earlier. There was one death during the active treatment phase that was not related to the study drug. A 63-year-old male patient with a history of pulmonary tuberculosis, randomised to the fluvastatin IR 40 mg qpm group, died as a result of haemoptysis. No serious adverse events were considered to be study drug-related, and there were no differences between the three treatment groups.

In total, 22 patients were discontinued from the study due to abnormalities in biochemical or haematological variables: five patients (3.5%) receiving fluvastatin XL 80 mg qpm, three patients (2.1%) receiving fluvastatin IR 40 mg qpm, and 14 patients (9.0%) receiving fluvastatin IR 40 mg bid; all these discontinuations were due to elevated levels of liver enzymes. Enzyme levels returned to normal following drug withdrawal. The incidence of clinically notable ALT/AST values (> 3 times upper limit of normal on two consecutive visits) were 1.4%, 1.4% and 7.2% for fluvastatin XL 80 mg qpm, fluvastatin IR 40 mg qpm and fluvastatin IR 40 mg bid, respectively (table 5). No clinically notable elevation in CK was observed in any treatment group.

The mean and median values for all biochemical and haema-

Table 4. Summary of clinical adverse events occurring with an incidence ≥ 3% during active treatment

Adverse event	Fluvastatin XL 80 mg qpm (n=139)		Fluvastatin IR 40 mg qpm (n=145)		Fluvastatin IR 40 mg bid (n=153)	
	Total	Drug related	Total	Drug related	Total	Drug related
No. of patients experiencing adverse events	107 (77.0%)	17 (12.2%)	104 (71.7%)	21 (14.5%)	111 (72.5%)	25 (16.3%)
Body as a whole – general disorders	28 (20.1%)	1 (0.7%)	27 (18.6%)	1 (0.7%)	30 (19.6%)	1 (0.7%)
Accidental trauma	12 (8.6%)	0	4 (2.8%)	0	11 (7.2%)	0
Influenza-like symptoms	6 (4.3%)	0	7 (4.8%)	0	6 (3.9%)	0
Allergy	4 (2.9%)	0	5 (3.4%)	0	3 (2.0%)	0
Chest pain	4 (2.9%)	1 (0.7%)	5 (3.4%)	1 (0.7%)	4 (2.6%)	0
Fatigue	2 (1.4%)	0	7 (4.8%)	0	2 (1.3%)	1 (0.7%)
Central and peripheral nervous system	20 (14.4%)	3 (2.2%)	16 (11.0%)	3 (2.1%)	13 (8.5%)	2 (1.3%)
Headache	10 (7.2%)	2 (1.4%)	7 (4.8%)	1 (0.7%)	9 (5.9%)	1 (0.7%)
Gastrointestinal system	41 (29.5%)	10 (7.2%)	43 (29.7%)	12 (8.3%)	41 (26.8%)	15 (9.8%)
Abdominal pain	10 (7.2%)	2 (1.4%)	14 (9.7%)	4 (2.8%)	8 (5.2%)	7 (4.6%)
Nausea	8 (5.8%)	4 (2.9%)	8 (5.5%)	4 (2.8%)	8 (5.2%)	1 (0.7%)
Diarrhoea	7 (5.0%)	2 (1.4%)	7 (4.8%)	0	11 (7.2%)	0
Vomiting	5 (3.6%)	1 (0.7%)	4 (2.8%)	1 (0.7%)	5 (3.3%)	0
Dyspepsia	4 (2.9%)	1 (0.7%)	10 (6.9%)	4 (2.8%)	12 (7.8%)	8 (5.2%)
Musculoskeletal system	38 (27.3%)	5 (3.6%)	30 (20.7%)	4 (2.8%)	34 (22.2%)	5 (3.3%)
Back pain	10 (7.2%)	1 (0.7%)	7 (4.8%)	0	5 (3.3%)	0
Arthropathy	9 (6.5%)	0	6 (4.1%)	0	12 (7.8%)	0
Myalgia	6 (4.3%)	2 (1.4%)	2 (1.4%)	0	5 (3.3%)	2 (1.3%)
Arthralgia	5 (3.6%)	0	4 (2.8)	3 (2.1%)	0	0
Respiratory system	48 (34.5%)	0	37 (25.5%)	1 (0.7%)	36 (23.5%)	0
Upper tract infection	29 (20.9%)	0	15 (10.3%)	0	22 (14.4%)	0
Sinusitis	9 (6.5%)	0	10 (6.9%)	0	8 (5.2%)	0
Coughing	4 (2.9%)	0	5 (3.4%)	0	3 (2.0%)	0
Rhinitis	4 (2.9%)	0	2 (1.4%)	0	5 (3.3%)	0
Pharyngitis	2 (1.4%)	0	3 (2.1%)	0	6 (3.9%)	0
Bronchitis	(0.7%)	0	7 (4.8%)	0	0	0
Skin and appendages	14 (10.1%)	2 (1.4%)	17 (11.7%)	0	11 (7.2%)	2 (1.3%)
Rash	5 (3.6%)	1 (0.7%)	4 (2.8%)	0	1 (0.7%)	0
Urinary system	15 (10.8%)	1 (0.7%)	9 (6.2%)	0	6 (3.9%)	1 (0.7%)
Urinary tract infection	11 (7.9%)	0	3 (2.1%)	0	3 (2.0%)	0

Key: XL = extended release; IR = immediate release; n = number of patients; qpm = every night; bid = twice-daily

tological variables were within the normal ranges at baseline and at end point, except for a few individual values. Although not drug-related, and consistent with the patients' underlying condition, two patients experienced ECG abnormalities. One patient (randomised to fluvastatin XL 80 mg qpm) had sinus bradycardia assessed as clinically significant; the patient's baseline ECG was, however, also abnormal. The second patient (randomised to fluvastatin IR 40 mg bid) developed a T-wave inversion interpreted as abnormal and clinically significant.

Discussion

More than six million patient-years of experience through clinical trial and clinical practice have established the efficacy and safety of the marketed fluvastatin IR formulation for lipid reduction. Fluvastatin is currently approved at starting doses of 20–40 mg/day, which are associated with mean reductions in LDL-C of 22–25%.[12] Some patients, however, require more aggressive lipid lowering to reach recommended LDL-C targets and, for these patients, titration to the maximal approved 40 mg bid dosage of fluvastatin IR may be necessary. Alternatively, the availability of fluvastatin as an XL formulation for a once-daily starting dose of 80 mg could provide additional flexibility in attempts to achieve lipid-lowering treatment goals.

The present study was one of three phase 3 trials conducted globally to evaluate the long-term safety and efficacy of fluvastatin XL 80 mg qpm compared with fluvastatin IR 40 mg qpm. In addition, the therapeutic equivalence of fluvastatin 80 mg qpm versus fluvastatin IR 40 mg bid was investigated. All three trials have given consistent results.[20,21]

The ability of fluvastatin XL 80 mg qpm to lower LDL-C levels was superior to that of fluvastatin IR 40 mg qpm (33.5% and 23.2%, respectively at week 24). Superiority of the XL formulation was seen at all timepoints analysed. The increase in efficacy achieved by doubling the dose of fluvastatin and modifying the

Table 5. Frequency of newly occurring, worsening or notable abnormalities of CK, AST and ALT

Laboratory variable	Fluvastatin XL 80 mg qpm (n=139) n (%)	Fluvastatin IR 40 mg qpm (n=145) n (%)	Fluvastatin IR 40 mg bid (n=153) n (%)
CK			
≥ 5 ULN–< 10 ULN	1 (0.7)	0	1 (0.7)
≥ 10 ULN	0	0	0
AST or ALT			
Notable*	2 (1.4)	2 (1.4)	11 (7.2)

Key: * Notable is > 3 ULN on two consecutive occasions; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase

formulation appeared to exceed the usual anticipated 6–7% point increase.[22] Fluvastatin XL 80 mg qpm was therapeutically equivalent to fluvastatin IR 40 mg bid. At week 24, reductions in LDL-C of at least 35% were achieved in 51% of patients receiving fluvastatin XL 80 mg qpm and in 48% of patients receiving fluvastatin IR 40 mg bid.

Significantly greater changes were also evident for HDL-C, LDL:HDL ratio, TC, apo A1 and apo B when fluvastatin XL 80 mg qpm was compared with fluvastatin IR 40 mg qpm. Treatment with fluvastatin XL 80 mg qpm was associated with an effect on the lipid profile equivalent to those seen with fluvastatin IR 40 mg bid treatment. However, the decrease in LDL:HDL ratio was significantly greater in the fluvastatin XL 80 mg qpm group.

HDL-C levels increased in all three treatment groups (10.2%, 7.9% and 5.0% for fluvastatin XL 80 mg qpm, fluvastatin IR 40 mg bid and fluvastatin IR 40 mg qpm, respectively). There were also clinically relevant reductions in TG levels (-14.6%, -14.3% and -10.7% for fluvastatin XL 80 mg qpm, fluvastatin IR 40 mg bid and fluvastatin IR 40 mg qpm, respectively). An interesting observation was the between-phenotype difference in the extent of HDL-C and TG alterations. For both these variables, changes were most evident among patients with mixed dyslipidaemia (Fredrickson type IIb). For example, in the fluvastatin XL 80 mg qpm group, HDL-C levels increased by 13.5% and TG levels fell by 20.1% in type IIb patients, compared with 7.8% and 11.2% respectively in the type IIa group.

Both decreased HDL-C and elevated TG levels are independent risk factors for coronary artery disease and, although statin therapy is principally aimed at lowering LDL-C levels, alterations in other lipid variables are also considered beneficial.[23,24] For example, in the Lipoprotein and Coronary Atherosclerosis Study (LCAS), patients with low initial HDL-C levels showed the greatest angiographic improvement with fluvastatin therapy.[25] Low HDL-C has been associated with a 40% increase in the risk of cardiovascular events, while increasing HDL-C is associated with a reduction in cardiovascular risk.[4]

Adverse events

Consistent with previously reported data, the proportion of patients for whom treatment was discontinued due to suspected study drug-related newly occurring or worsening adverse events was low in all three treatment groups; the lowest frequency occurred in patients receiving the XL 80 mg formulation of fluvastatin (3.6%).[26]

The cerivastatin experience has shown that cases of probable early rhabdomyolysis have a mean CK about 3,000 mU/ml. The upper limit of normal for CK in this study was 120 mU/ml, and thus, no patient had a CK level above 1,200 mU/ml. We can therefore conclude from our data that there was no evidence of myopathy (as measured by clinically notable CK elevations) in any of the study participants. As these study patients (hypercholesterolaemics) are relatively active, the majority of cases of musculoskeletal pain reported were reported to be related to acute physical situations (i.e. gardening, sports such as cycling, weightlifting, tennis etc.).

Fluvastatin XL 80 mg qpm has a much longer half-life (seven hours) than fluvastatin IR 40 mg bid (two hours) and 50% less systemic exposure over a 24-hour period.[27] The gradual and sustained delivery of fluvastatin from the fluvastatin XL tablet avoids hepatic saturation.[28] Theoretically, this should result in a better safety profile for fluvastatin XL than IR. Hepatoxicity has been reported in less than 1% of patients receiving high doses of statins; none of the treatments in this study raised any safety concerns with respect to liver enzymes. Indeed, there were fewer instances of critical and/or clinically notable increases of liver enzymes in the fluvastatin XL 80 mg qpm and IR 40 mg qpm groups compared with the fluvastatin IR 40 mg bid group. These results support a pooled analysis from three double-blind studies, which showed that fluvastatin XL was more efficacious than IR 40 mg formulations, while having a tolerability that was similar to placebo.[17]

Many patients receive statin therapy on a long-term basis, and compliance for a once-daily treatment is likely to be greater than for a twice-daily dosing regimen. The availability of the XL 80 mg formulation of fluvastatin, which induced therapeutically equivalent – and for some variables greater – changes in lipoprotein levels compared with the same dose given twice-daily, will undoubtedly be beneficial for the optimal management of patients with primary hypercholesterolaemia.

Conclusions

The fluvastatin XL 80 mg qpm formulation is significantly more effective than fluvastatin IR 40 mg qpm, and therapeutically equivalent to fluvastatin IR 40 mg bid, in reducing LDL-C levels. Other lipid variables, including HDL-C, TC, LDL:HDL ratio, apo A1 and apo B, improved significantly more in patients receiving fluvastatin XL 80 mg qpm compared with those receiving fluvastatin 40 mg qpm. The incidence of adverse events was low across all treatments, with no unexpected events. Fluvastatin XL 80 mg qpm therefore appears to be a suitable treatment for patients with type II hypercholesterolaemia.

Conflict of interest

None. This study was supported by a research grant from

Key messages

- The fluvastatin XL 80 mg qpm formulation was significantly more effective than fluvastatin IR 40 mg qpm, and therapeutically equivalent to fluvastatin IR 40 mg bid, in reducing LDL-C levels in patients with type II hypercholesterolaemia
- Fluvastatin XL 80 mg qpm significantly improved HDL-C, TC, LDL:HDL ratio, apo A1 and apo B compared with fluvastatin 40 mg qpm.
- Fluvastatin XL 80 mg qpm was well tolerated throughout the study, with no cases of myopathy
- Fluvastatin XL 80 mg qpm appears to be a suitable treatment for patients with type II hypercholesterolaemia

Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

Fluvastatin study group

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