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APPLICATION NUMBER:
21-192

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-192

Application Type: NDA

Sponsor: Novartis

Proprietary Name: Lescol XL

Investigator: Multiple (Not named)

USAN Name: Fluvastatin

Category: HMG-CoA reductase inhibitor

Route of Administration: oral

Reviewer: S.W. Shen, M.D.

Review Date: 8/21/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
Dec. 8, 1999	Dec. 9, 1999	NDA	

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments
April 18, 1997	IND 53,109	
Feb. 11, 1992	NDA 20-261	

EXECUTIVE SUMMARY:

Lescol (fluvastatin sodium) is a water-soluble cholesterol-lowering agent which acts to specifically inhibit HMG-CoA reductase. It was approved for marketing in the US in December 1993. The usual recommended dose was 20 -40 mg capsules once daily and 40 mg BID. The current clinical program was undertaken to register an 80mg modified release (MR) once a day dosage form of fluvastatin.

the Agency stipulated that the 80mg MR formulation must demonstrate superiority (i.e. > 6% reduction in LDL-C) to fluvastatin IR. Placebo-controlled trials were not required; instead at least two well-controlled trials with adequate treatment duration were needed to meet this criterion. In 3 pivotal Phase 3 studies involving 1680 patients, fluvastatin MR 80mg QPM was found to be superior in reducing LDL-C (>6%) to fluvastatin IR 40mg QPM after 24 weeks of treatment. Administration of MR 80mg QPM also resulted in statistically significantly greater reductions in plasma total cholesterol (Total-C), apolipoprotein B (Apo B) compared to treatment with IR 40mg QPM. Only a trend for greater reduction in TG and greater in increases in HDL-C and apolipoprotein A1 were seen. No new unexpected adverse events were reported. The incidence of adverse events, the primary lab. safety parameters of AST/ALT elevations from baseline between MR 80mg and IR 40mg QPM treatments were similar. No patient treated with MR 80mg QPM developed CK>10 x ULN and there were no cases of rhabdomyolysis. 120-day Safety Update of the Extension studies up to 52 weeks and Second Safety Update of additional patients showed essentially similar safety profiles.

Fluvastatin MR 80mg was superior to IR 40mg QPM in lowering the LDL-C levels in patients with Type IIa and IIb hyperlipoproteinemia. It can be given as a starting dose, and it is a useful addition to the currently marketed dose formulations.

OUTSTANDING ISSUES:

Efficacy in increasing HDL-C in patients with Type IIa and IIb hyperlipoproteinemia.

RECOMMENDED REGULATORY ACTION:

MR 80mg formulation (extended release tablets)

Approvable.

SIGNATURES:

Medical Reviewer:

LSI

Date 9/21/00

Medical Team Leader:

LSI

Date 10/10/00

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List of abbreviations:

ANOVA	Analysis of variance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ALT	Alaline aminotransferase (formerly SGPT)
AST	Aspartate aminotransferase (formerly SGOT)
BID	Bis in diem/twice a day
BMI	Body mass index
CAD	Coronary Artery Disease
CI	Confidence interval
CK	Creatine kinase
DL	Deciliter
HDL-C	High-density lipoprotein-cholesterol
HLP	Hyperlipoproteinemia
HMGRI	HMG-CoA reductase inhibitor
IR	Immediate release
ITT	Intent-to-treat
Kg	Kilogram
LDL-C	Low-density lipoprotein-cholesterol
Lp (a)	Lipoprotein a
LS	Least aquare
LSM	Least square mean
m	meter
mg	miliigram
MR	Modified release
MX	matrix formulation
NCEP	National Cholesterol Education Program
NDA	New drug application
PK	Pharmacokinetic
QPM	once daily at bedtime
Sd	Standard deviation
TOTAL-C	Total-cholesterol
TG	Triglycerides
TSH	Thyroid stimulating hormone
VLDL-C	Very-low-density-lipoprotein-cholesterol
ULN	Upper limit of normal
UTI	Urinary tract infecion

Introduction and Background:**Administrative Background:**

The current clinical program was undertaken to register an 80mg modified release (MR) once a day dosage form of fluvastatin.

the Agency had stipulated certain requirements for the approval of the 80mg MR formulation:

1. The Agency stipulated the 80mg MR formulation must demonstrate superiority (i.e. 6% greater reduction in LDL-C) to fluvastatin 40mg IR. Placebo-controlled trials were not required, instead, at least two-well-controlled trials with adequate treatment duration were needed to meet this criterion.
2. It was required that at least 500 patients be exposed to fluvastatin MR 80mg QPM matrix tablets for 6 months.
3. It was required that at least 500 patients be exposed to fluvastatin MR 80mg QPM matrix tablets for 6 months.
4. If unusual adverse events were observed/reported during the 6-month treatment period, additional long-term data would be collected up to one year in at least 100 patients.

Other health authorities (BfArM/Germany, MC/United Kingdom and HPB/Canada) required:

1. That the 80mg MR formulation demonstrates therapeutic equivalency to fluvastatin 40mg IR BID. Therapeutic equivalency to fluvastatin was defined by these authorities as no more than 5% difference in absolute mean percent change in LDL-C from baseline between 40mg BID of fluvastatin and the 80mg MR dose.
2. The BfArM (Germany health authority) requested the identification of a specific patient population which will benefit with a 80mg MR matrix tablet a starting dose

Clinical Background:

Multiple epidemiological studies have established that elevation of serum cholesterol, specifically LDL-C, is a major risk factor for development of cardiovascular disease. HMG-Co-A reductase inhibitors have been shown to slow the progression of coronary atherosclerosis and reduce the incidence of myocardial infarction, cardiovascular as well as total mortality. The National Cholesterol Education Program (NCEP) has established treatment goals for LDL-C, which depend on an individual's risk for cardiovascular disease.

Fluvastatin is a water soluble cholesterol-lowering agent which acts through the inhibition of 3-HMG-CoA reductase. It was approved for marketing in the U.S. on 12/31/93.

Chemistry/Manufacturing Controls:

The chemical name is [R*,S*-(E)]-(+)-7-[13-4-fluorophenyl]-1-(1-methylethyl)-1H-indol-2-yl]-3,5, dihydroxy-6-heptenoic acid, monosodium salt. For structural formula and other details, please see Chemistry Review.

Human Pharmacology/Pharmacokinetics:

Please see Biopharmacology Review.

Description of Clinical Data Sources:

This NDA submission contained efficacy and safety data from 7 trials in patients with primary hypercholesterolemia (N = 2040; Phase IIa Study XUO-W253, Phase IIb Studies XUO-F201, XUO-F252, XUO-F253; and pivotal Phase III Studies XUO-F302, XUO-F351 and XUO-F353) and 3 healthy volunteer studies (XUO-W251, XUO-W252 and XUO-W351).

The efficacy and safety analyses derived from the pivotal Phase III 24-week trials (Studies XUO-F302, XUO-F351 and XUO-F353) were comprised of patients treated with fluvastatin 80 mg MR QPM (_____ tablet selected for marketing), fluvastatin IR 40 mg QPM, and fluvastatin IR 40 mg BID. Additional safety data were submitted on 4/6/00 in the 120-day Safety Update (the cutoff date was 12/31/1999) which contained pooled data from two completed long-term 6-month open-label extension trials, XUO-F351-E01 and XUO-F353-E01 in patients with primary hypercholesterolemia. A second Safety Update containing data from 3 new studies, (generated between January 1, 2000 and May 31, 2000), was submitted on 9/7/2000 and received on 9/8/2000.

A total of 1680 patients were randomized in the 3 pivotal well-controlled trials (XUO-F302-E-00, XUO-F351-E-00, and XUO-F353-E-00), including:

- 857 fluvastatin 80 mg MR QPM patients
- 505 fluvastatin 40 mg IR QPM patients
- 330 fluvastatin 40 mg IR BID patients

Integrated Summary of Safety:

This Integrated Summary of Safety only contains safety data in sponsor's original NDA submitted on 12/8/1999. The sponsor did not incorporate the safety data contained in the 120-Day Update or the safety data in the Second Safety Update submitted on 9/7/2000 into the original NDA submission. The safety data in these two submissions will be evaluated in the Individual Study Section.

- A. The number of Patients:** The majority of the safety analyses were conducted on two patient groups: the Phase IIb and Phase III trials patient group. Summary of studies used for safety evaluation is shown below:

Study #	Treatment groups	# of Patients	Active treatment
XUO-F201	Fluvastatin MR 80mg QPM Fluvastatin MR 80mg QPM Fluvastatin MR 80mg QPM Fluvastatin IR 40 BID	70	4 weeks
XUO-F252	Fluvastatin MR 80mg QPM Fluvastatin 80mg QPM Fluvastatin 80mg pelletized cap. QPM Fluvastatin 80mg pelletized cap. QPM Fluvastatin IR 40 mg BID	129	4 weeks
XUO-F253 -E00	Fluvastatin MR 80mg QPM Fluvastatin MR 160 mg (2 80mg 8-hr matrix tabs) QPM Fluvastatin IR 40mg QPM	121	6 weeks
XUO-F302 -E00; 51 Centers In Europe	Fluvastatin MR 80mg QPM Fluvastatin IR 40mg QPM Fluvastatin IR 40mg BID	691	24 weeks
XUO-F351-E00, 30 Centers U.S.A.	Fluvastatin MR 80mg QPM Fluvastatin IR 40mg QPM	552	24 weeks
XUO-F353-E00 29 Centers (U.S, Canada, etc)	Fluvastatin MR 80mg QPM Fluvastatin IR 40 mg QPM Fluvastatin IR 40 mg BID	437	24 weeks
XUO-F351 -E01	Fluvastatin MR 80 mg QPM Fluvastatin IR 40mg QPM	390	28 weeks
XUO-F353- E01	Fluvastatin MR 80 mg QPM Fluvastatin IR 40mg QPM Fluvastatin IR 40 mg BID	357	28 weeks
XUO-F-354- E00	Fluvastatin MR 80 mg QPM Atorvastatin 10 mg capsule QPM Simvastatin 40 mg capsule QPM Pravastatin 40 mg capsule QPM	523	16 weeks
XUO-F355- E00	Fluvastatin MR 80 mg QPM Fluvastatin IR 40 mg capsule QPM	173	16 weeks
XUO-F356- E00	Fluvastatin MR 80 mg QPM Fluvastatin IR 40 mg capsule QPM	219	16 weeks

B. Duration/extent of exposure: The focus is on the Phase III studies and the extension studies since these patients had the longest exposure to MR 80 mg QPM.

A total of 749/851 fluvastatin MR 80mg treated patients completed 24 weeks of therapy on the Phase III trials (studies XUO-F302-E00, F351-E00 and F353-E00). Studies XUO-F351-E01 and XUO-F353-E01 represented the extensions from these Phase III 24-week double blind studies. Patients who have been randomized to fluvastatin MR 80 QPM continued to receive this dose up to an additional 28 weeks. A total of 390 patients entered the extension study and 351 patients completed the full 52-weeks of treatment.

An additional 357 patients, initially randomized to fluvastatin IR either 40 mg QPM or 40 mg BID in the Phase III 24-week studies entered the 28-week open-label E-01 extensions and received fluvastatin 80 mg MR for up to 28 weeks. A total of 327 patients completed the 28-week open-label extensions.

1. 749 patients were treated with MR 80 mg QPM for 24 weeks.
2. 327 patients were treated with MR 80 mg QPM for 28 weeks.
3. 351 patients completed the full 52-weeks of treatment with MR 80 mg QPM.
4. The Second Safety Update, which was received on 9/8/2000, did not include Study Protocols of the 3 completed Phase IIIb double-blind, 16-week studies. The details of the studies are therefore unknown. Apparently a total of 324 patients received fluvastatin MR 80 mg QPM in these 3 studies and 293 patients completed the 16-week studies. If the protocols followed the protocols of Phase III studies with 4-week diet-run-in period, then the exposure to MR 80 mg QPM was only 12 weeks.

C. Demographics of the safety population: Summary of selected demographics and baseline characteristics Phase III and IIb trials in safety analyzable patients (all randomized patients with at least one safety evaluation after the administration of active study medication) as provided by the Sponsor is shown below:

	Fluva. MR 80mg QPM N=912; n (%)	Fluva. IR 40mg QPM N=643; n (%)	Fluva. IR 40mg BID N=368; n (%)
Age: <65	664 (72.8)	397 (73.1)	293 (79.6)
≥65	248 (27.2)	146 (26.9)	75 (20.4)
Sex: Male	434 (47.6)	246 (45.3)	175 (47.6)
Race: Caucasian	830 (91.0)	499 (91.9)	339 (92.1)
Black	40 (4.4)	19 (3.5)	7 (1.9)
Other	42 (4.6)	25 (4.6)	22 (6.0)
BMI (kg/m²)			
<30	739 (81.0)	444 (81.8)	315 (85.6)
≥30	172 (18.9)	97 (17.9)	51 (13.9)
Weight (mean; kg)	76.0	76.3	75.3
Prior HMGRI Use			
Yes	391 (42.9)	225 (41.4)	160 (43.5)
No	499 (54.7)	316 (58.2)	167 (45.4)
Missing data	22 (2.4)	2 (0.4)	41 (11.1)
Baseline LDL-C			
<190 mg/dL	502 (55.6)	295 (54.3)	198 (53.8)
190-≤220 mg/dL	250 (27.4)	146 (26.9)	96 (26.1)
>220 mg/dL	160 (17.5)	102 (18.8)	74 (20.1)
Phenotype			
IIa TG (mg/dL) <200	633 (69.4)	390 (71.8)	265 (72.0)
IIb TG (mg/dL) ≥200	279 (30.6)	153 (28.2)	103 (28.0)

The three treatment groups were generally comparable with respect to baseline demographic and lipid values. In all treatment groups, the majority of patients ($\geq 70\%$) used at least one concomitant medication during the active treatment phase of the studies, and there were no clinically relevant differences across treatment groups.

D. Patient disposition:

- The majority of safety analyzable patients in all treatment groups completed the studies: fluvastatin MR 80mg QPM=88.7%, fluvastatin IR 40mg QPM=90.1%, fluvastatin IR 40mg BID=84.2%, and fluvastatin MR 160mg QPM=90.0%. Patients who discontinued during the active treatment period (safety analyzable patients) in Phase IIb and III trials (as provided by the sponsor) are shown below:

Reason for discontinuation	Fluva. MR 80mg QPM N=912		Fluva. IR 40mg QPM N=543		Fluva. IR 40mg BID N=368		Fluva. MR 160mg QPM N=40		Fluva. MR 80mg Other forms n=137	
	N	(%)	N	(%)	N	(%)	N	(%)	n	(%)
Total	103	(11.3)	54	(9.9)	58	(15.8)	4	(10.0)	3	(2.2)
Adverse event	37	(4.1)	14	(2.6)	15	(4.1)	3	(7.5)	3	(1.5)
Abn. Lab. value	21	(2.3)	12	(2.2)	18	(4.9)	0	(0)	0	(0)
Death	1	(0.2)	1	(0.2)	0	(0)	0	(0)	0	(0)
Protocol violation	2	(0.2)	2	(0.4)	2	(0.5)	0	(0)	0	(0)
Withdrew consent	31	(3.4)	11	(2.0)	13	(3.5)	0	(0)	0	(0)
Lost to follow-up	7	(0.8)	10	(1.8)	5	(1.4)	1	(2.5)	1	(0.7)
Other	5	(0.5)	4	(0.7)	5	(1.4)	0	(0)	0	(0)

The most common reasons for discontinuation from active treatment were adverse events, withdrawal of consent and abnormal lab. values. Discontinuations due to adverse events (as provided by the sponsor) are shown below:

	Fluva. MR 80mg QPM N=912; n (%)		Fluva. IR 40mg QPM N=543; n (%)		Fluva. IR 40mg BID N=368 n (%)	
Total # of patients	36	(3.9)	14	(2.6)	16	(4.3)
Gastrointestinal system	18	(2.0)	6	(1.1)	8	(2.2)
Abdominal pain	6	(0.7)	2	(0.4)	4	(1.1)
Dyspepsia	4	(0.4)	0		2	(0.5)
Diarrhea	5	(0.5)	1	(0.2)	2	(0.5)
Nausea	4	(0.4)	3	(0.6)	2	(0.5)
Musculo-skeletal system	5	(0.5)	2	(0.4)	1	(0.3)
Myalgia	1	(0.1)	1	(0.2)	1	(0.3)
Back pain	1	(0.1)	1	(0.2)	0	
Liver & biliary system	4	(0.4)	1	(0.2)	2	(0.5)
Hepatic enzymes increases	2	(0.2)	1	(0.1)	1	(0.3)
Hepatic function abn.	1	(0.1)	0		1	(0.3)

The fluvastatin IR 40mg BID group had the highest incidence of discontinuation due to adverse events and discontinuation due to abnormal lab. values. The treatment groups were similar with regard to other specific reason for discontinuation.

E. Adverse Events:

- 1. Death and other serious or clinically significant adverse events:** patients who died, experienced serious or clinically significant adverse events or discontinued prematurely because of them in Phase IIb and III trials is shown below:

	Fluva.MR 80mg QPM N=912		Fluva.IR 40mg QPM N=543		Fluva. IR 40mg BID N=368	
	N	(%)	N	(%)	N	(%)
# of patients with AES	552	(60.5)	322	(59.3)	219	(59.5)
# discontinued due to AES	36	(3.9)	14	(2.6)	16	(4.3)
# of patients with SAEs	34	(3.7)	9	(1.7)	14	(3.8)
# discontinued due to SAEs	6	(0.7)	0		3	(0.8)
# of patients died						
Study/Patient	Age/sex	Treatment/duration	Cause of death	Comment		
XUO-F351 010-0012	69/male	Fluva.MR 80mg QPM 3 mos.post-random.	Metastatic lung cancer	Occurred after discontinuation		
XUO-F353	63/male	Fluva. IR 40mg QPM 52 days post-random.	Haemoptysis pulmonary TB	Med. Hx of CAD & pulmonary TB		

The 2 deaths were unlikely to be due to study drug.

There was a statistically significant difference in the overall frequency of SAEs (Serious Adverse Events) between the fluvastatin IR 40mg QPM and 80mg MR QPM treatment groups. The 80mg MR QPM and the 40mg IR BID had the same frequency. It is of interest to note that these differences may be due to the frequency of SAEs in Study F351 (5.4% for 80 MR vs. 1.1% for IR 40 mg), but not seen in study F302 (2.9% vs. 2.8%) and F353 (2.9% vs. 2.8%). Study F351 was different from the 2 other studies by being a 30-Center-US study in which patients were randomized only to two groups: fluvastatin MR 80 mg QPM (n=370) and fluvastatin IR 40 mg QPM (n=185). The Inclusion/Exclusion criteria, the demographic and other baseline characteristics of the patients were quite similar in the all 3 Phase III studies. The reason for the reported difference in SAEs is not obvious. However, none of the SAEs was assessed as being study drug related. Overall, there were no clinically significant differences among the treatment groups with regard to the incidence of SAEs.

- 2. Incidence rates of most frequently reported (3%) adverse events in most frequently affected body systems defined as >10% in Phase IIb and III trials are shown below (table provided by the sponsor):**

	Fluva.MR 80mg QPM N=912		Fluva.IR 40mg QPM N=543		Fluva. IR 40mg BID N=368	
	N	(%)	N	(%)	N	(%)
Total patients with AES	552	(60.5)	322	(59.3)	219	(59.5)
Resp. system disorders	209	(22.9)	119	(21.9)	64	(17.4)*
URI infections	114	(12.5)	53	(9.8)	33	(9.0)
Sinusitis	32	(3.6)	27	(5.0)	8	(2.2)
Body as a whole	165	(18.1)	90	(16.6)	52	(14.1)
Influenza-like symptoms	65	(7.1)	35	(6.4)	21	(5.7)
Accidental trauma	38	(4.2)	15	(2.8)	11	(3.0)
Total patients with GI and/or Musculo-skeletal disorders	308	(33.8)	186	(34.3)	113	(30.7)
GI system disorders	187	(20.5)	112	(20.6)	77	(20.9)
Abdominal pain	34	(3.7)	28	(5.2)	18	(4.9)
Dyspepsia	32	(3.5)	29	(5.3)	20	(5.4)
Diarrhea	30	(3.3)	15	(2.8)	17	(4.6)
Nausea	23	(2.5)	19	(3.5)	11	(3.0)
Musculo-skeletal disorders	172	(18.9)	101	(18.6)	47	(12.8)**
Back pain	43	(4.7)	28	(5.2)	9	(2.4)
Myalgia	35	(3.8)	9	(1.7)	8	(2.2)
Arthropathy	29	(3.2)	23	(4.2)	13	(3.5)

• $p < 0.05$ for fluvastatin MR 80mg QPM vs. fluvastatin 40mg BID, for events with incidence $> 5\%$.

** $p < 0.001$ for fluvastatin MR 80mg QPM vs. fluvastatin IR 40mg BID for events with incidence $> 5\%$.

Although there were statistically significantly higher incidences of respiratory system disorders and musculo-skeletal events with the 80mg MR treatment group vs. the IR 40mg BID group, the majority of the events were mild or moderate in nature. The percentage of patients with severe adverse events were 5.6%, 3.3% and 6.5% for fluvastatin MR 80mg QPM, fluvastatin IR 40mg QPM and fluvastatin IR 40mg BID respectively. Therefore, the difference between the 80mg MR and 40mg IR-BID was not considered clinically significant.

- The body systems with the highest occurrence** of suspected study-drug related newly occurring or worsening adverse events were GI., musculo-skeletal, central and peripheral nervous system disorders. The frequency of such adverse events are shown below:

	Fluva.MR 80mg QPM N=912		Fluva.IR 40mg QPM N=543		Fluva. IR 40mg BID N=368	
	N	(%)	N	(%)	N	(%)
Gastrointestinal disorders	65	(7.1)	34	(6.3)	32	(8.7)
Diarrhea	17	(1.9)	1	(0.2)	4	(1.1)
Dyspepsia	16	(1.8)	14	(2.6)	12	(3.3)
Musculo-skeletal disorders	22	(2.4)	12	(2.2)	6	(1.6)
Myalgia	17	(1.9)	5	(0.9)	3	(0.8)
Central & peripheral nervous system disorders	14	(1.5)	8	(1.5)	4	(1.1)
Headache	7	(0.8)	5	(0.9)	3	(0.8)

The overall frequency of gastrointestinal and musculo-skeletal disorders was similar across treatment groups although incidence of myalgia was higher in the MR 80mg QPM group. It is reassuring that no patient had CK>10ULN in the MR 80 mg QPM group (see table below.)

4. **Primary safety laboratory evaluations:** The accumulated experience in this class of drugs, HMG-CoA reductase inhibitor, has demonstrated that the adverse events of particular clinical concern are abnormal liver function tests and CK elevation. The number of patients with various levels of CK, AST and ALT elevations during active treatment of Phase IIb and III trials is shown below (Table modified from the one provided by the sponsor):

Laboratory variable	Fluva. MR 80mg QPM N=912		Fluva. IR 40mg QPM N=543		Fluva. IR 40mg BID N=368	
	N	(%)	N	(%)	N	(%)
CK						
<2 ULN	865	(94.8)	520	(95.8)	350	(95.1)
≥2 ULN <5 ULN	42	(4.6)	15	(2.8)	14	(3.8)
≥5 ULN <10 ULN	3	(0.3)	4	(0.7)	2	(0.5)
>10 ULN	0	(0.0)	2	(0.4)	0	(0)
AST or ALT						
≤1.15 ULN	570	(62.5)	384	(70.7)	232	(63.0)
>1.15 ULN <2 ULN	235	(25.6)	116	(21.4)	81	(22.0)
≥2 ULN <3 ULN	44	(4.8)	16	(2.9)	24	(6.5)
>3 ULN not consecutively	44	(4.8)	16	(2.9)	13	(3.5)
>3 ULN on ≥2 occasions	17	(1.9)	9	(1.7)	16	(4.3)
# discont. Due to ASAT/ALAT abn.	28	(3.0)	13	(2.4)	19	(5.2)
# discont. due to >3ULN on ≥2 occa.	14	(1.5)	7	(1.3)	13	(3.5)
# discont. due to single >3ULN	12	(1.3)	5	(0.9)	5	(1.3)
# discont. due to non-cons.>3ULN	2	(0.2)	1	(0.2)	1	(0.3)

For CK elevations, no patient had CK>10 ULN in either the 80mg MR or 40mg IR BID treatment groups compared to 2 patients in the 40mg IR QPM group.

- In Study XUO-F302-E00, patient 077-021 experienced elevated CK of 1245 mU/mL on Day 28 (normal -120 mU/mL). He reported intense physical

activity two days before. Concomitant elevations of ASAT (42mmU/mL) and ALAT ((31 mU/mL) were noted on Day 29. He was asymptomatic. He discontinued the study drug on Day 33 and from the study on Day 36. Two weeks after discontinuation, the CK level was <2xULN.

2. In Study XUO-F351-E00, patient 09 007 (JJG): 60-year-old female experienced elevation of CK of 1844 mU/mL (normal 0-120 mU/mL) on Day 133. Her AST/ALT were 73/35 mU/mL at the same time. No other clinically significant lab abnormalities and patient complained only of mild tenderness and stiffness. Study drug was stopped and patient was discontinued from the study one week later. All values returned to normal.

For AST/ALT elevations >3 ULN, the incidence rates in the MR 80mg and IR 40mg treatment groups were 1.9% and 1.7% respectively; compared to 4.3% in IR 40mg BID group. The rate of discontinuations due to AST/ALT elevations was similar between the MR 80mg QPM (3.0%) and 40mg IR QPM groups (2.4%) but was higher (5.2%) in the 40mg IR BID group.

The graphic presentation by the sponsor (not shown) of the AST/ALT mean data by timepoint indicated an increase from baseline at Week 4 with a gradual return to baseline by Week 12. This is consistent with the pattern of other statins.

The incidences of AST/ALT>3xULN (in the above table) by demographic /baseline characteristics are examined below: (The post-text table 11.4-1 provided by the sponsor is misleading. The following table was prepared in consultation with J. Todd Sahlroot, Ph.D., Mathematical Statistician.)

Characteristic	Fluva. MR 80mg QPM N=912		Fluva. IR 40mg QPM N=543		Fluva. IR 40mg BID N=368	
	N	(%)	N	(%)	N	(%)
Age Group:						
<65 yrs	15/664	(2.3)	7/397	(1.8)	13/293	(4.4)
≥65 yrs	2/248	(0.8)	2/146	(1.4)	3/75	(4.0)
Sex:						
Male	2/434	(0.5)	1/246	(0.4)	6/175	(3.4)
Female	15/478	(3.1)	8/297	(2.7)	10/193	(5.2)
Prior HMGRI Use:						
Yes	5/391	(1.3)	3/225	(1.3)	5/160	(3.1)
No	12/499	(2.4)	6/316	(1.9)	11/167	(6.9)
Missing data: 22						
BMI category (kg/m²):						
≤30	16/739	(2.2)	8/444	(1.8)	15/315	(4.8)
>30	1/172	(0.6)	1/97	(1.0)	1/51	(2.0)
Missing data: 1						
Baseline LDC-C (mg/dL)						
<190	6/502	(1.2)	7/295	(2.4)	10/198	(5.1)
190-<220	7/250	(2.8)	2/146	(1.7)	5/96	(5.2)
≥220	4/160	(2.5)	0	(0.0)	1/74	(1.4)
Total number	17	(1.9)	9	(1.7)	16	(4.3)

Overall, for the demographic/baseline variables listed in the table, there were no evident subgroup effects of the incidence rates of AST/ALT >3xULN. There appears to be an apparent difference between males and females. Without a placebo-controlled group, no definitive conclusion can be drawn. However, when individual patient data were reviewed to determine whether there was any correlation between sex, weight and incidence of AST/ALT >3xULN, no relationship was found.

Individual patients with AST/ALT >3xULN in the Phase III studies are evaluated below:

1. In Study XUO-F353, 2 patients each in MR 80mg QPM and IR 40mg QPM groups and 11 patients in IR 40mg BID group had elevations >3ULN on 2 consecutive occasions of AST/ALT.

(1). MR 80mg QPM:

- a. Patient 23 010 (—): a 67-year-old female experienced elevated AST (444 mU/mL, normal range 8 to 22) and ALT (340 mU/mL, normal range 5 to 25 mU/mL) on Day 28. The patient discontinued study drug on Day 30. AST and ALT decreased to 163/372 mU/mL on Days 48. On Day 84, AST decreased to 29 mU/mL and ALT to 26 mU/mL. She had not been exposed to HMGRI within the year.
- b. Patient 24 003 (—): a 34-year-old female experienced elevated AST (281 mU/mL) and ALT (458 mU/mL) on Day 83. Four days earlier, the patient complained of severe epigastric burning, RUQ pain and mild scleral icterus. The study drug was stopped and repeat AST/ALT values 3 days later were 54/250. A hepatitis screen was negative but multiple small stones were seen in her gallbladder. Post-operative enzymes returned to normal levels.

(2). IR 40mg QPM:

- a. Patient 13 032 (—): a 55-year-old female experienced elevations of AST (43 mU/mL) and ALT (101 mU/mL) on Day 115. Repeat ALT on Day 119 was 112 mU/mL. Study drug was discontinued on Day 121 and she was discontinued from the study on Day 127. Follow-up tests on Day 143 showed AST/ALT of 35/64 mU/mL. She had been exposed to HMGRI previously within the year.
- b. Patient 25-007 (—): a 58 year-old male experienced elevated AST (249 mU/mL) and ALT (284 mU/mL) on Day 28. Patient complained of increase in urination only. Patient was discontinued from study on Day 58. Repeat tests showed AST/ALT of 17/40 mU/mL on Day 65 and 15/13 on Day 84. Patient had been exposed to HMGRI within the year.

(3). IR 40mg BID:

- a. Patient 04 028 (—): a 74-year-old female experienced elevations of AST (211 mU/mL) and ALT (255 mU/mL) on Day 28. Study drug was stopped on Day 29. Repeat tests on Day 36, showed AST/ALT of 27/51 mU/mL and on Day 43, the values were 20/20 mU/mL. Study drug was resumed on Day 44. On Day 54,

AST/ALT were 70/97 mU/mL. Study drug was stopped on Day 56 and discontinued from the study on Day 66. 2 weeks after stopping the drug, the values were 31/43 mU/mL respectively for AST/ALT. Patient did not have any clinical symptom other than mild intermittent heartburn.

- b. Patient 01 011 (—): a 74-year-old female experienced elevations of AST (171 mU/mL) and ALT (306 mu/mL) on Day 28. Repeat AST/ALT values one week later were 160/236. The study drug was stopped and patient was terminated from the study. 14 days later the AST/ALT values were 31/29 mU/mL.
- c. Patient 06 008 (—): a 60-year-old female experienced elevations of AST (157 mU/mL) and ALT (287 mU/mL) on Day 34. Repeat AST/ALT values 10 days later were 202/286. Study drug was stopped. Patient had no symptoms other than alkaline phosphatase was elevated at 272 (normal 32-72). Patient was terminated from the study. 39 days after discontinuation from the drug, AST/ALT were 19/17.
- d. Patient 96 051 (—): a 59-year-old female experienced elevations of AST (100 mU/mL) and ALT (197 mU/mL) on Day 56. A repeat AST/ALT values 2 days later were 63/138. Study drug was stopped 2 days later and discontinued from the study 19 days later. Patient was asymptomatic and AST/ALT decreased to 22/30.
- e. Patient 08-066 (—): a 49-year-old male experienced elevations of AST (79 mU/mL) and ALT (98 mU/mL) on Day 32. Three days later, AST decreased to 51 mU/mL but ALT remained at 116 mu/mL. The study drug was stopped and patient was discontinued from the study on Day 45. The AST/ALT values decreased to 26/29 mU/mL on repeat tests. Other than mild indigestion, patient was asymptomatic.
- f. Patient 09 063 (—): 59-year-old male experienced elevations of AST (246 mU/mL) and ALT (356 mU/mL) on Day 27. Study drug was stopped on Day 29. Repeat values were 40/231 on Day 36 and patient was discontinued from the study on Day 53. Follow-up values were 17/23 and patient was asymptomatic.
- g. Patient 21 020 (—): 70-year-old female experienced elevations of AST (95 mU/mL) and ALT (189 mU/mL) on Day 127. Study drug was stopped on Day 128. AST/ALT were repeated weekly until 28/45 were obtained 20 days after discontinuation of the study drug.
- h. Patient 21-028 (—): 51-year-old male experienced elevations of AST (136 mU/mL) and ALT (356 mU/mL) on Day 29. Study drug was stopped on Day 32. No follow-up lab. values were recorded.
- i. Patient 21-029 (—): 42-year-old male experienced elevation of AST (33 mU/mL) and ALT (48 mU/mL) on Day 64. Repeat values were 46/70 on Day 94. Patient's total bilirubin and LDH were also reported to be elevated at 1.34 mg/dL (normal: 0.1-1.0 mg/dL) and 101 mu/ml (normal: 40-100 mu/m) respectively. Study drug was stopped and patient was discontinued from the study on Day 101. Serial follow-up lab. values were conducted at the local lab. but results were not reported.
- j. Patient 54 004 (—): 51-year-old male experienced elevated AST (142 U/mL) and ALT (117 mU/mL) on Day 28. Patient complained of abdominal pain and

study drug was stopped on Day 30. Repeat AST/ALT values were 83/181 on Day 31 and 33/76 on Day 38. Follow-up values were normal by Day 48.

- k. Patient 31 006 (—): 57-year-old female experienced elevated AST (200 mU/mL) and ALT (1175 mU/mL) on Day 28. Repeat values were 65/101 on Day 36. Although patient was asymptomatic, study drug was stopped. Serial follow-up AST/ALT values were 26/28 on Day 80.

The IR 40 mg BID group had 11 patients with AST/ALT elevations $>3\times$ ULN compared to 2 each for the MR 80 mg QPM and IR 40 mg QPM groups. The reason(s) for this difference is not obvious. And this difference was not found in study XUO-F302-E00. It probably accounted for the higher over-all incidence of AST/ALT elevations $>3\times$ ULN in the 40 mg BID group (5.2%) compared the MR 40 mg QPM group (3.0%) and IR 40 mg QPM group (2.4%).

2. In Study XUO-F351-E00, There were 14 patients who had elevated AST/ALT $>3\times$ ULN on 2 consecutive occasions.

- (1). **MR 80mg QPM:** There were 14 patients in the MR 80 mg QPM group discontinued from the study due to abnormal transaminase elevations. 5/14 (patients 021-0017, 026-0001, 028-0005, 029-0038 and 016-0007) discontinued after only a single instance of AST/ALT $>3\times$ ULN. There were 9 patients who had elevated AST/ALT $>3\times$ ULN on 2 consecutive occasions. None of the patients had clinical symptoms or elevated bilirubin levels. Without exception, AST/ALT values returned to normal after discontinuation from the study drug.
- (2). **IR 40 mg QPM:** There were 5 patients who had elevated AST/ALT $>3\times$ ULN on 2 consecutive occasions. 4 of the patients had no clinical symptoms and values returned to normal. The fifth patient, patient 20 013 (—) was a 60-year-old female who experienced elevated AST (254 mU/mL) and ALT (272 mU/mL) on Day 30. Study drug was stopped. Repeat values 2 days later were 100/316. Patient complained of nausea, heartburn, diarrhea and dark urine. Alkaline Phosphatase and bilirubin were also elevated at 174 mu/ml (normal=32-72) and 1.7 mg/dL (normal=0.10-1.10 mg/dL) respectively. Patient was discontinued from the study. Follow-up values were 33/50 for AST/ALT and 113/0.7 for alkaline phosphatase and bilirubin. The sponsor stated that no further clinical/lab. data were available.

3. In Study XUO-F302-E00, 5 patients each in the MR 80 mg IR 40 mg BID groups and 2 patients in the 40 mg QPM group had AST/ALT elevations $>3\times$ ULN on 2 consecutive occasions:

- (1). **MR 80mg QPM:** There were 5 patients who had elevated AST/ALT $>3\times$ ULN on 2 consecutive occasions. None of the patients had clinical symptoms or elevated bilirubin. Without exception, AST/ALT values returned to normal after discontinuation of the study drug.
- (2). **IR 40mg QPM:** There were 2 patients who had elevated AST/ALT $>3\times$ ULN

on 2 consecutive occasions. On study drug discontinuation, transaminase levels were essentially normal.

- (3). **IR 40mg BID:** Two patients (012-007, 031-034) had elevated AST/ALT on Day 28. After study was stopped, the values returned to near normal levels.

However, the following patients had a different clinical course.

Patient 082-014: 66-year-old female presented with jaundice and elevated AST(239 mU/mL) /ALT (333 mU/mL) on Day 14. The study drug was stopped and she was discontinued from the study the same day. The abnormalities resolved 3 weeks after discontinuation.

Patient 085-016: 36-year-old male experienced elevated AST (57 mU/mL) and ALT (113 mU/mL) on Day 169. Repeat values on Day 176 were 49/95. The transaminase elevations were not accompanied by any clinical signs/symptoms or any other lab. abnormalities. Two weeks after study completion, the values of AST/ALT were still 68/101. The sponsor had no further information/data on this patient.

Patient 111-004: 60-year-old male experienced elevated AST (146 mU/mL) and ALT (217 mU/mL) on Day 60. Repeat values were 131/179 on Day 65. Study drug was stopped on Day 70 and was admitted to the hospital on Day 76 with a diagnosis of acute cholecystitis and choledocholithiasis. An open cholecystectomy was performed with good postoperative results. Patient was discontinued from the study in Day 102.

5. Secondary safety variables: Secondary lab. variables included hematology, biochemistry and urinalysis parameters.

- 1. Hematology:** The hematologic variables measured included RBC, WBC with differential and platelet count. The mean and median values for all hematologic variables were within normal range at Baseline and Endpoint, and there was no clinically significant differences among the 3 treatment groups. No more than 1.1% of the patients in any of the treatment group had abnormal hematological lab. values. Furthermore, all these individual cases of significant abnormalities were transient in nature, not associated with other abnormalities or symptoms. There were judged by the investigators of little clinical significance.
- 2. Chemistry:** There were no clinically significant differences among the treatment groups in the mean and median values of the biochemistry variables at either Baseline or Endpoint. Across all secondary chemistry safety parameters, the incidence rates of newly occurring or worsening abnormalities was $\leq 3.3\%$ in the 3 treatment groups. The incidence rates of clinically significant abnormalities was $\leq 0.9\%$ in the 3 treatment groups, and no clinically significant differences among the treatment groups were observed. There were 4 patients with increased total bilirubin levels as already described in patients with AST/ALT elevations. 2/4 patients (Patient 24-003 and patient 111-004) had gallstones and bilirubin levels returned to normal post-surgery. One patient (patient 20-013) had normal level after discontinuation from the study drug. Only one patient (patient

patients had statistically significant less AST/ALT elevations $>3 \times \text{ULN}$ on 2 consecutive occasions than fluvastatin IR 40mg BID-treated patients ($p < 0.05$). This was also the case for number of patients who discontinued due to abnormal AST/ALT values. There was no difference in the incidence rates of the primary lab. safety parameters of AST/ALT or CK elevations between patients with or without prior use of HMGRI.

5. Secondary lab. safety parameters (These include hematology, biochemistry and urinalysis parameters): There were no clinically significant differences among the treatment groups in the mean and median values at either Baseline or Endpoint. There were individual cases of abnormal variables. All these were either transient in nature or not abnormally sufficient to be clinically significant.

In conclusion, there was no difference in the incidence rates of adverse events, the primary lab. safety parameters of AST/ALT or CK elevations and secondary lab. safety abnormalities across demographic subgroups of patient with primary hypercholesterolemia in terms of gender, age, BMI and with or without prior use of HMGRI. Therefore, Fluvastatin MR 80 mg QPM is safe and can be administered as a starting dose.

Review of Individual Clinical Studies:

The principal clinical 3 Phase III studies, XUO-F353 E-00, XUO-F302 E-00 and XUO-F351 E00 were reviewed for safety and efficacy. Safety evaluations were included in the Integrated Summary of Safety. Only the efficacy evaluation will be presented.

Study XUO-F353 E00 and Study XUO-F302 E00:

Study XUO-F353 E00 and Study XUO-302 E00 were 28-week prospective, double-blind, randomized, observer-blind to lipid variables, parallel group, multicenter study in patients with primary hypercholesterolemia (Type IIa or IIb). Study XUO-F353 E00 consisted of 29 centers in the U.S., Canada, Turkey, S. Africa, Australia and New Zealand. Study XUO-F302 E00 consisted of 51 centers in Germany, Italy, Netherlands, Czech Republic, Spain, UK, Poland and Sweden.

I. Objectives:

Efficacy:

The efficacy objectives were to demonstrate superiority, the lipid lowering effect of fluvastatin 80mg MR formulation QPM compared to IR 40mg QPM, and to demonstrate non-inferiority between 80mg MR formulation QPM and 40mg IR formulation BID.

Safety:

The safety objective was to assess the safety and tolerability of fluvastatin 80mg

MR formulation compared to 40mg IR administered once or twice daily.

II. Patient Selection:

1. Inclusion Criteria:

- * Males and non-pregnant, non-lactating females at least 18 years of age.
- * Patients who were eligible and able to participate in the study and who consented to do so after the purpose and nature of the investigation had been explained to them.
- * Patients who, after previous dietary counseling, had been following a fat and cholesterol restrictive diet as advised by the European Atherosclerosis Society (EAS), or NCEP Step 1 or Step II diets for at least 4 weeks before the entry into the placebo/dietary stabilization lead-in period (Week -4).
- * Patients who had elevated plasma LDL-C level despite dietary therapy, defined as a LDL-C level at or above 160 mg/dL (4.1 mmol/l) at two visits during the placebo/dietary lead-in period (Weeks -4 and -2, Visits 1 and 2, respectively).
- * The value of LDL-C at Week 0 was not to serve as an inclusion criterion. If these criteria were not satisfied, then one additional lipid sample could have been performed between Week -2 and 0 (designated as Week -1, Visit 3), in order to enable the patient to qualify for entry into the active treatment period of the study. The LDL-C value of any 2 of these 3 visits must have been at or above 160 mg/dL (4.1 mmol/l).
- * Patients who had plasma triglyceride levels at or below 400 mg/dL (4.5 mmol/l) at each of the lipid qualifying visits during the placebo/dietary lead-in period (Weeks -4, and -2 or -1). One optional visit was allowed for qualification during Week -1.
- * Both the LDL-C and triglyceride criteria had to be met at the same two qualifying visits.

2. Exclusion Criteria:

- * Homozygous familial hypercholesterolemia; type I, III, IV or V hyperlipoproteinemia (WHO classification).
- * Previous participation in other investigative trials involving slow release fluvastatin dosage forms, regardless of treatment arm assignment.
- * Pregnant or lactating women, or women of child bearing potential who were not using or complying with an approved mechanical method of contraception. A woman was considered to be of childbearing potential unless she was post-hysterectomy, one or more years post-menopausal or one or more years post-tubal ligation. All women of child bearing potential must have had a negative pregnancy test at the beginning of the placebo/dietary-lead in period (Week -4/Visit 1), and before initiating active treatment (Week 0/Visit 4). Relevant to

this exclusion criterion, at the time of the Investigators Meeting, a clarification was provided. Specifically, patients who were stable (at least 3 months) on Depo-Provera regimen were eligible for study participation.

- * Hyperlipidemia secondary to other causes.
- * Any surgical or medical condition which might have significant, altered the absorption, distribution, metabolism or excretion of any drug. Patients with a history of urinary obstruction or prostate problems were allowed providing they had recovered after surgical or medical treatment and no further intervention was foreseen.
- * Serum CK levels greater than 2 times ULN. If serum CK was between 2 and 5 times ULN at Week -4 or Week -2, one retest was allowed at Week -1, in order for the patient to qualify for study entry provided all other criteria were fulfilled. Serum CK must have been ≤ 2 times ULN at two of three evaluations obtained between Week -4 and 0 (i.e. Wk -4, Wk -2 or Wk -1) to be eligible for further study participation. If serum CK was greater than 5 times ULN at any timepoint between Weeks -4 and 0, the patient was excluded from further study participation.
- * Liver injury as indicated by transaminase serum levels either the ALAT/SGPT or ASAT/SGOT was between 1.5 and 2 times ULN at Week -4 or Week -2, one retest was allowed at Week -1, in order for the patient to qualify for study entry, provided all other criteria were fulfilled. Additionally, the ALAT and ASAT had to be ≤ 1.5 times ULN at two of three evaluations obtained between Week -4 and 0 (i.e. Wk -4, Wk -2 or Wk -1) to be eligible for further study participation. If any of these values were greater than 2 times ULN at any timepoint between Weeks -4 and 0, the patient was excluded from further study participation.
- * Impaired renal function as indicated by serum creatinine levels were between 1.5 and 2 times ULN at Week -4 or Week -2, one retest was allowed at Week -1, in order for the patient to qualify for study entry provided all other criteria were fulfilled. The serum creatinine had to be ≤ 1.5 times ULN at two of three evaluations obtained between Week -4 and 0 (i.e. Wk -4, Wk -2 or Wk -1) to be eligible for further study participation. If serum creatinine was greater than 2 times ULN at any timepoint between Weeks -4 and 0, the patient was excluded from further study participation.
- * Serum TSH levels outside the normal range at Week -4 (Visit 1). In the case plasma TSH was below the normal range, or above but < 2 times ULN, one retest was permitted at Week -2 (Visit 2), provided all other criteria were fulfilled. No retest was allowed if TSH level was ≥ 2 times ULN at Week -4. The retest TSH value at Visit 2 had to be within the normal range for patients to qualify for randomization. The retest was introduced with Amendment No. 1.
- * Any acute illness or severe trauma in the three months prior to Week -4/Visit 1.
- * Congestive heart failure, severe or unstable angina pectoris. This exclusion criterion was clarified at the Investigators Meeting. After discussion, it was

agreed patients with stable and clinically controlled congestive heart failure would be eligible for study participation.

- * Myocardial infarction, major surgery, or angioplasty during the 6 months prior to Week -4/Visit 1.
- * Poorly controlled or uncontrolled hypertension (mild-to-moderate hypertensive patients well controlled by antihypertensive therapy were allowed to enter the study only if the dose of antihypertensive medication was constant for at least 2 months before the entry into the trial, and it is felt unlikely that a change in dosage will be necessary during the trial).
- * Prior or current muscle disease of any type.
- * Clinically significant ophthalmological abnormalities such as glaucoma or vision limiting cataracts. Patients with normal intraocular pressure following surgical/medical treatment were eligible, however.
- * Within the last two years, a history of drug abuse or a history of alcohol consumption greater than 65 ml pure alcohol per day - that is: per day, more than six 125 ml glasses of wine or two glasses of spirits.
- * Exposure to any investigational new drug within 30 days of study entry (Week -4/Visit 1) or ingestion of any drug known to be toxic to a major organ system (such as those producing blood dyscrasias, nephrotoxicity, hepatotoxicity or neurotoxicity) within 12 weeks prior to the study entry (Week -4).
- * Ingestion of any agent specifically intended to reduce serum lipid levels, such as, but not limited to HMGRI, clofibrate, gemfibrozil, cholestyramine, colestipol, niacin, or any fish-oil derivative at least 4 weeks before the first lipid determination (Week -4), or ingestion of probucol within one year prior to entry of the patient into the study.
- * Posicor (mibefradil dihydrochloride) use within 10 weeks prior to study entry (Week -4). This criterion was eliminated per Amendment No. 1 (see complete details in Section 4).
- * Patients currently treated with, or expected to require cyclosporine or continuous systemic erythromycin. Brief courses of systemic or topical erythromycin for sporadic infections/illness will not result in exclusion.
- * History of being resistant to lipid-lowering medications. Known hypersensitivity or intolerance to any HMGRI, i.e. elevated transaminases, myositis.
- * Excessive obesity defined as BMI at or above 32 kg/m^2 (BMI = body-weight in Kg divided by height in meters squared; 1 kg = 2.2 lbs. and 1 meter = 39.4 in). This criterion was revised to exclude patients at or above 35 kg/m^2 (per Amendment No. 1).
- * Uncontrolled hyperthyroidism.

*Any signs of mental dysfunction or other factors (including language problems) likely to limit the ability of the patient to cooperate with the performance of the study.

3. Interruption or discontinuation from treatment:

There were no specific allowances for interruption of study medication. Patients had to take at least 80% of the prescribed doses during the 24-week active treatment period in order to be eligible for the per protocol analysis (see Section 6 for further details). Reasons for discontinuing patients from the study included the following:

Pregnancy and/or positive pregnancy test.

Elevations of transaminase levels >3 times the upper limit of normal range on 2 consecutive or non-consecutive assessments.

Any clinical or biochemical evidence of liver injury other than hypertransaminasemia.

CK elevations \geq 10 times ULN on a single occasion.

Significant adverse events which would preclude the patient continuing in the study.

Administrative reasons.

III. Study Design and Procedures:

Both studies were multicenter, double-blind, randomized, observer-blind to lipid data, parallel group, positive-control study. The studies began with a 4-week placebo/dietary run-in period during which time patients stopped taking any lipid-lowering medications and followed AHA Step 1 diet. At the end of the 4-week run-in, patients were randomized:

A. Study F353: 442 patients were randomized, 434 were included in the primary efficacy analysis and 437 were included in the safety analysis. The dosage groups were:

1. 141 patients to fluvastatin MR 80mg QPM,
2. 146 patients to fluvastatin IR 40mg QPM,
3. 155 patients to fluvastatin IR 40mg BID.

B. Study F302: 695 patients were randomized, 621 (89.4%) completed the 24-week active treatment. 691 were included in the safety analysis and 688 were included in the efficacy analysis. The dosage groups were:

1. 250 patients on fluvastatin MR 80mg QPM,
2. 125 patients on fluvastatin IR 40mg QPM,
3. 125 patients on fluvastatin IR 40mg BID.

The detailed study procedures are shown below:

	Week	-8	-4	-2	-1	0	2	4	8	12	16	20	24
Inclusion/exclusion			*	*	*	*							
Dietary compliance			*	*		*	*	*	*	*	*	*	*
Physical exam			*			*				*			*
Vital signs			*	*		*	*	*	*	*	*	*	*
Complete lab			*			*				*			*
Lipids, short lab.			*	*	*	*	*	*	*	*	*	*	*
TSH			*										
Pregnancy screen			*			*				*			*
Dispense medication			*	*		*		*	*	*	*	*	
Drug accountability				*		*		*	*	*	*	*	*
Concomitant medication		*	*	*	*	*	*	*	*	*	*	*	*
Adverse events assessment				*	*	*	*	*	*	*	*	*	*

IV. Patient Characteristics: The “intent-to-treat (ITT) population” or “primary efficacy analysis population” includes all randomized patients with a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement for a given parameter. The “safety-analyzable population” includes all randomized patients with at least one safety evaluation after the administration of active study medication.

Table IV: Selected Demographic and Baseline Characteristics valid for efficacy population:

		Fluva. MR 80mg QPM		Fluva. IR 40mg QPM.		Fluva. IR 40mg BID	
		N	%	N	%	N	(%)
Study F353		N=141		N=146		N=155	
Age:	<65	100	(70.9)	109	(74.7)	122	(78.7)
	>65	41	(29.1)	37	(25.3)	33	(21.3)
Sex:	Male	57	(40.4)	68	(46.6)	78	(50.3)
	Female	84	(59.6)	78	(53.4)	77	(49.7)
Mean weight(kg) at enrollment		76.8		75.5		77.0	
Body mass index (kg/m ²)		27.1		26.4		26.8	
Prior HMGRI use:	Yes	77	(54.6)	66	(45.2)	82	(52.9)
	No	64	(45.4)	80	(54.8)	73	(47.1)
Baseline LDL-C (mg/dL):	<190	81	(57.4)	86	(58.9)	92	(59.4)
	190-<220	32	(22.7)	36	(24.7)	24	(23.9)
	≥220	28	(19.9)		(16.4)	26	(16.8)
Baseline HDL-C (mg/dL):	<35	6	(4.3)	7	(4.1)	5	(3.2)
	≥35	135	(95.7)	140	(95.9)	150	(96.8)
Phenotype	IIa (TG<200mg/dL)	97	(68.9)	108	(74.0)	97	(62.5)
	IIb (TG>200mg/dL)	44	(31.2)	38	(26.0)	58	(37.4)

Study F302		N=3346	N=174	N=175
Age:	<65	264 (76.3)	123 (70.7)	138 (78.9)
	≥65	82 (23.7)	51 (29.3)	37 (21.1)
Sex:	Male	156 (45.1)	71 (40.8)	79 (45.1)
	Female	190 (54.9)	103 (59.2)	96 (54.9)
Mean weight(kg) at enrollment		73.4	73.9	74.3
Body mass index (kg/m ²)		26.7	26.5	26.5
Prior HMGR I use:	Yes	137 (39.6)	68 (39.1)	79 (45.1)
	No	209 (60.9)	106 (60.9)	96 (54.9)
Baseline LDL-C (mg/dL):	<190	170 (49.1)	85 (48.9)	86 (49.1)
	190-220	105 (30.3)	48 (27.6)	45 (25.7)
	≥220	66 (19.1)	41 (23.6)	42 (24.0)
Baseline HDL-C (mg/dL):	<35	7 (2.0)	3 (1.7)	8 (4.6)
	≥35	334 (96.5)	171 (98.3)	165 (94.3)

Across the 3 treatment groups, the demographic and baseline characteristics were similar. Of the 437 patients randomized, 412 completed Study XUO-F353-E00 and of the 695 patients randomized to double-blind treatment, 621 completed Study XUO-F302-E00. The disposition of the patients were included in the Integrated Summary of Safety.

V. Efficacy:

A. Study XUO-F302:

Primary Efficacy Results-Reduction in LDL-C: Least square Mean percent change from baseline in LDL-C at Endpoint (all randomized patients) is shown below:

Parameter	Fluva. MR 80mg QPM N=341	Fluva. IR 40mg QPM, N=174	Fluva. IR 40mg BID N=173
Baseline mean (mg/dL)	198.9	202.8	199.4
Least Square mean % change	-32.6	-24.3	-32.7
SE % change	0.93	1.20	1.18

At the Endpoint, the fluvastatin MR 80mg QPM group had an 8.3% greater least square mean percent reduction in LDL-C than the fluvastatin IR 40mg QPM group ($p < 0.001$). The 95% confidence interval of the difference in mean percent LDL-C reduction between the groups was 5.7% to 10.8%. These results indicate that doubling the dose of fluvastatin reduced least-square mean LDL-C by at least an additional 6% over a 24-week treatment period.

Secondary Efficacy Results: Least-square means (SE) from Baseline to Endpoint in selected lipid parameters (all randomized patients) are shown below:

Secondary Efficacy parameter	Fluva. MR 80mg QPM N=341	Fluva. IR 40mg QPM; N=174	Fluva. IR 40mg BID N=173
HDL-C	8.1% (0.96)	6.2% (1.74)	6.7% (1.22)
Total cholesterol	-23.0% (0.69)*	-16.9% (0.89)	-23.5% (0.88)
TG	-12.3% (1.87)	-8.2% (2.41)	-13.1% (2.38)
Apo A1	7.8% (0.93)	6.5% (1.21)	6.4% (1.19)
Apo B	-25.2% (0.88)*	-18.8% (1.14)	-25.0% (1.12)

* Significantly different from fluvastatin IR 40mg QPM ($p < 0.05$; 2-way ANOVA with treatment and center as factors.)

B. Study XUO-F353

Primary Efficacy Results-Reduction in LDL-C: Least Square Mean percent change from baseline in LDL-C at Endpoint (all randomized patients) is shown below:

Parameter	Fluva. MR 80mg QPM N=139	Fluva. IR 40mg QPM; N=143	Fluva. IR 40mg BID N=152
Baseline mean (mg/dL)	199.3	193.1	195.2
Least square mean % Change	-33.3	-23.2	-30.7
SE % change	1.42	1.37	1.31

At the Endpoint, the fluvastatin MR 80mg QPM group had an 10.1% greater mean percent reduction in LDL-C than the fluvastatin IR 40mg PQM group ($p < 0.001$). The 95% confidence interval of the difference in mean percent LDL-C reduction between the groups was 6.7% to 13.5%. These results indicate that doubling the dose of fluvastatin reduced least-square mean LDL-C by at least an additional 6% over a 24-week treatment period.

Secondary Efficacy Results: Least-square means (SE) from Baseline to Endpoint in selected lipid parameters (all randomized patients) are shown below:

Secondary Efficacy parameter	Fluva. MR 80mg QPM N=139	Fluva. IR 40mg QPM; N=143	Fluva. IR 40mg BID N=152
HDL-C	10.8% (1.1)*+	4.6% (1.0)	7.3% (1.0)
Total cholesterol	-23.4% (1.06)*	-16.7% (1.02)	-22.0% (0.98)
TG	-16.0% (2.68)	-11.7 (2.58)	-14.6% (2.47))
Apo A1	11.2 (1.07)*+	5.9% (1.05)	8.3% (1.07)
Apo B	-23.3% (1.30)*+	-16.4% (1.27)	-21.9% (1.19)

* Significantly different from fluvastatin IR 40mg QPM ($p < 0.05$)

+ Significantly different from fluvastatin IR 40mg BID ($p < 0.05$)

In this study, both HDL-C and Apo A1 in the MR 80mg QPM group were statistically different from IR QPM and IR BID groups ($p < 0.05$). This is in contrast to the two other studies. The baseline lipid values of all 3 studies were similar, particularly with regard to baseline HDL-C levels. The reason for the different finding in this study is not obvious.

Study XUO-F351:

Study XUO-F351 was a 28-week prospective, double-blind, randomized, observer-blind to lipid variables, parallel group, multicenter study in patients with primary hypercholesterolemia (Type IIa or IIb).

I. Objectives:

Efficacy:

The efficacy objectives were to demonstrate the lipid lowering effect of fluvastatin 80mg MR formulation QPM compared to IR 40mg QPM.

Safety:

The safety objective was to assess the safety and tolerability of fluvastatin 80mg MR formulation compared to 40mg IR administered once daily.

II. Patient Selection: The Inclusion and Exclusion criteria were identical to that of Study XUO-F353.

III. Study Design and Procedures: Identical to that of Study XUO-F353 except patients were randomized to two groups: fluvastatin MR 80mg QPM ($n=370$) and fluvastatin IR 40mg QPM ($n=185$).

IV. Patient Characteristics: The "intent-to-treat (ITT) population" or "primary efficacy analysis population" includes all randomized patients with a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement for a given parameter. The "safety-analyzable population" includes all randomized patients with at least one safety evaluation after the administration of active study medication.

		Fluva. MR 80mg QPM N=370		Fluva. IR 40mg QPM N=185	
		N	%	N	%
Age:	<65	258	(69.7)	136	(73.5)
	≥65	112	(30.3)	49	(26.5)
Sex:	Male	193	(52.2)	88	(47.6)
	Female	177	(47.8)	97	(52.4)
Mean weight(kg) at enrollment		78.1		78.7	
Body mass index (kg/m ²)		27.2		27.7	
Prior HMGRI use:	Yes	154	(41.6)	75	(40.5)
	No	215	(58.1)	108	(58.4)
Baseline LDL-C (mg/dL):	<190	217	(58.6)	108	(58.4)
	190-220	100	(27.0)	49	(26.5)
	≥220	53	(14.3)	28	(15.1)
Baseline HDL-C (mg/dL):	<35	22	(5.9)	16	(8.6)
	≥35	348	(94.1)	169	(91.4)
Phenotype	Ia (TG<200mg/dL)	230	(62.2)	115	(62.2)
	Ib (TG≥200mg/dL)	140	(37.8)	70	(37.8)

Across the 2 treatment groups, the demographic and baseline characteristics were similar. The baseline lipid values of TG and HDL-C were also similar to the Studies F353 and F302.

V. Efficacy:

Primary Efficacy Results-Reduction in LDL-C: Least Square Mean percent change from baseline in LDL-C at Endpoint (all randomized patients) is shown below:

Parameter	Fluva. MR 80mg QPM, N=369	Fluva. IR 40mg QPM, N=183
Baseline mean (mg/dL)	191.4	193.6
Least square mean % Change	-31.0	-23.0
SE % change	0.80	1.07

At the Endpoint, the fluvastatin MR 80mg QPM group had an 8.0% greater least square mean percent reduction in LDL-C than the fluvastatin IR 40mg QPM group ($p < 0.001$). The 95% confidence interval of the difference in mean percent LDL-C reduction between the groups ranged from 5.6% to 10.4%. These results indicate that doubling the dose of fluvastatin reduced LDL-C by at least an additional 6% over a 24-week treatment period.

Secondary Efficacy Results: Least-square means (SE) from Baseline to Endpoint in selected lipid parameters (all randomized patients) are shown below:

Secondary Efficacy parameter	Fluva. MR 80mg QPM N=369	Fluva. IR 40mg QPM; N=183	p-value
HDL-C	8.6% (0.8)	7.2% (1.0)	0.238
Total cholesterol	-22.0% (0.6)	-16.2% (0.8)	<0.001
TG	-14.1% (1.7)	-9.3 (2.3)	0.062
Apo A1	+8.1 (0.7)	+7.1 (1.0)	0.350
Apo B	-23.03% (0.8)	-16.34% (1.07)	<0.001

Only Total-C and Apo B demonstrated statistical significance between the treatment groups of MR 80mg QPM vs. IR 40mg QPM.

Extension Studies: Studies XUO-F351-E01 and XUO-F353-E01 represented the extensions from the Phase III 24-week double blind studies. Patients who have been randomized to fluvastatin MR 80 QPM continued to receive this dose up to an additional 28 weeks. A total of 390 patients entered the extension study and 351 patients completed the full 52-weeks of treatment. Additional 357 patients, initially randomized to fluvastatin IR either 40 mg QPM or 40 mg BID in the Phase III 24-week studies entered the 28-week open-label E-01 extensions and received fluvastatin 80 mg MR for up to 28 weeks. A total of 327 patients completed the 28-week open-label extensions. These two studies were submitted in the 120-day Safety Update. Only safety data were included. No unusual/unexpected adverse events were observed/reported. The 120-day Safety Update showed that the incidences of adverse events and discontinuations due to adverse events were similar between the Extension Trials and Phase III trials. For the primary safety parameters of CK and ASAT/ALAT levels, lower rates of AST/ALT elevations (>3x ULN on 2 occasions) and discontinuations due to abnormal AST/ALT elevations were observed since the elevations occurred during the first 12 weeks of treatment.

The Second Safety Update: This safety update contained data from 11 completed and on-going studies. Only the 3 completed 16-week Phase IIIb double-blind studies with fluvastatin MR 80 mg QPM are relevant to this NDA and will be reviewed. These 3 studies are listed below:

Study #	Treatment groups	# of patients randomized/treated	Population
XUO-F354-E00	Fluvastatin MR 80 mg QPM Atorvastatin 10 mg QPM; Simvastatin 40 mg QPM; Pravastatin 40 mg QPM	523	Type IIa and IIb
XUO-F355-E00	Fluvastatin MR 80 mg QPM Fluvastatin IR 40 mg QPM	173	Type IIa and IIb
XUO-F356-E00	Fluvastatin MR 80 mg QPM Fluvastatin IR 40 mg QPM	219	Mixed dyslipidemia

A. The number of patients/duration of exposure: No protocols were submitted. The details of the studies are therefore unknown. Apparently a total of 324 patients

received fluvastatin MR 80 mg QPM in these 3 studies and 293 patients completed the 16-week studies.

- B. **Demographics of the study:** The patients in Study XUO-F355 were older i.e. 60.5% were <65 and 39.5% were \geq 65 years of age, compared to 72.8% were < 65 and 27.2% were \geq 65 years of age in the ISS and the 120-day safety update. Other demographic and baseline characteristics were similar.
- C. **Patient disposition:** Approximately 7.8% of the safety analyzable patients were discontinued for various reasons from these trials. In all these studies, the most common reason for discontinuation for any treatment group was adverse events. Followed by "other". The rate of discontinuation due to adverse events in the fluvastatin MR 80 mg QPM group (9.4% in Study XUO-F354, 5.8% in Study -F355 and 5.5% in Study -F356) were higher than in the pooled analysis of studies included in ISS (4.1% in Phase IIb and III studies) and the 120-day safety update.
- D. **Deaths and other serious or clinically significant adverse events:** There were no deaths in these studies. The number of patients with Serious Adverse Events (SAEs) in the fluvastatin MR 80 mg QPM groups were 0% in Study XUO-F354, 2.3% in Study -F355 and 0.9% in Study -F356 compared to 3.7% in ISS. The number of patients discontinued due to SAEs were 0% in Study XUO-F354, 1.2% in Study -F355 and 0.9% in Study -F356 compared to 0.7% in the pooled analysis of studies included in ISS.
- E. **The overall frequency of adverse events due to fluvastatin MR 80 mg QPM treatment** was lower in these studies than in the pooled analysis of studies included in ISS (60.5%) and in the 120-day safety update (73.1%). However, the adverse event profile was similar to the profile obtained from the controlled Phase IIb and Phase III studies. In particular, the incidence of gastrointestinal and musculo-skeletal adverse events were similar, and no unexpected events were seen in Studies XUO-F354, -F355 and -F356.
- F. **For the primary lab. safety parameters:** No patient treated with MR 80 mg QPM had CK>10xULN and no case of rhabdomyolysis. The overall combined frequencies of patients with AST/ALT >3xULN in these studies (7/324=2.2%) were higher than those observed in ISS (1.9%) and 120-day safety update (0.3%). However, this rate is comparable to those reported with other statins.

In conclusion, the Second Safety Update on 3 completed Phase IIIb studies demonstrated similar safety profile as reported in ISS and 120-day safety update, and no unexpected events were reported.

Integrated Summary of Efficacy.

This Integrated Summary of Efficacy consists of data from a total 6 Phase IIb and Phase III controlled clinical trials on patients with primary hypercholesterolemia (Type IIa or IIb). Of these 3 Phase III studies (Studies XUO-F302, XUO-F351 and XUO-F353) with an active treatment duration of 24 weeks are considered to be adequate and well-controlled to support the efficacy analysis for the 80 mg MR fluvastatin dose regimen. The 3 Phase III studies are shown below:

Study	Type of control	Treatment	# of patients	Active treatment
F302	Fluva. IR 40mg QPM & BID	Fluva. MR 80mg QPM	695 randomized	24 weeks
F351	Fluva. IR 40mg QPM	Fluva. MR 80mg QPM	555 randomized	24 weeks
F353	Fluva. IR 40mg QPM & BID	Fluva. MR 80mg QPM	442 randomized	24 weeks

The 3 pivotal Phase III studies had the following common features:

1. They were all double-blind and observer-blind to lipid variables, parallel group, multicenter, active-controlled studies in patients with hypercholesterolemia. (Type IIa or IIb).
2. All had a 4-week placebo/diet lead-in period followed by a 24-week active treatment period.
3. Qualified patients were males (46.5%) and non-pregnant, non-lactating females (53.5%) at least 18 years of age with a constantly elevated plasma LDL-C > 160mg/dL and plasma TG ≤ 400mg/dL during the placebo/diet lead-in period.
4. The objective of all 3 studies was to demonstrate therapeutic superiority of fluvastatin MR 80mg QPM over fluvastatin IR 40mg QPM, and to demonstrate tolerability of initial dosing with MR 80mg QPM as opposed to titration.
5. All randomized patients with a baseline measurement and at least one post-baseline measurement were included in the intent-to-treat analysis. Percent change from baseline in LDL-C and HDL-C were analyzed by means of an analysis of variance with treatment group and trial as the factors. Two treatment comparisons were included: fluvastatin MR 80mg QPM vs. fluvastatin IR 40mg BID, and fluvastatin MR 80mg QPM vs. fluvastatin IR 40mg QPM.

The efficacy results of the primary and secondary efficacy parameters of the 3 pivotal Phase III studies were reviewed in the Individual Clinical Studies Section. The pooled analysis of the 3 pivotal Phase III studies is reviewed below.

Pooled analysis of Phase III studies: Data from XUO-F302, XUO-F351 and XUO-F353 were pooled by concatenating the efficacy data of all randomized patients from the 3 studies. This consists of 849 patients treated with fluvastatin MR 80mg QPM, 500 patients treated with fluvastatin IR 40mg QPM, and 325 patients treated with fluvastatin IR 40mg BID.

A. Primary Efficacy Parameter: LDL-C least square mean percent change (SE) from Baseline to Endpoint (all randomized patients):

Treatment group	N	Baseline mean	LS mean change (SE)
Fluvastatin MR 80mg QPM	849	195.7	-32.2% (0.51)
Fluvastatin IR 40mg QPM	500	196.7	-23.8% (0.64)
Fluvastatin IR 40mg BID	325	197.4	-31.6% (0.83)

1. LDL-C reductions from Baseline to Endpoint by gender and age group are shown below:

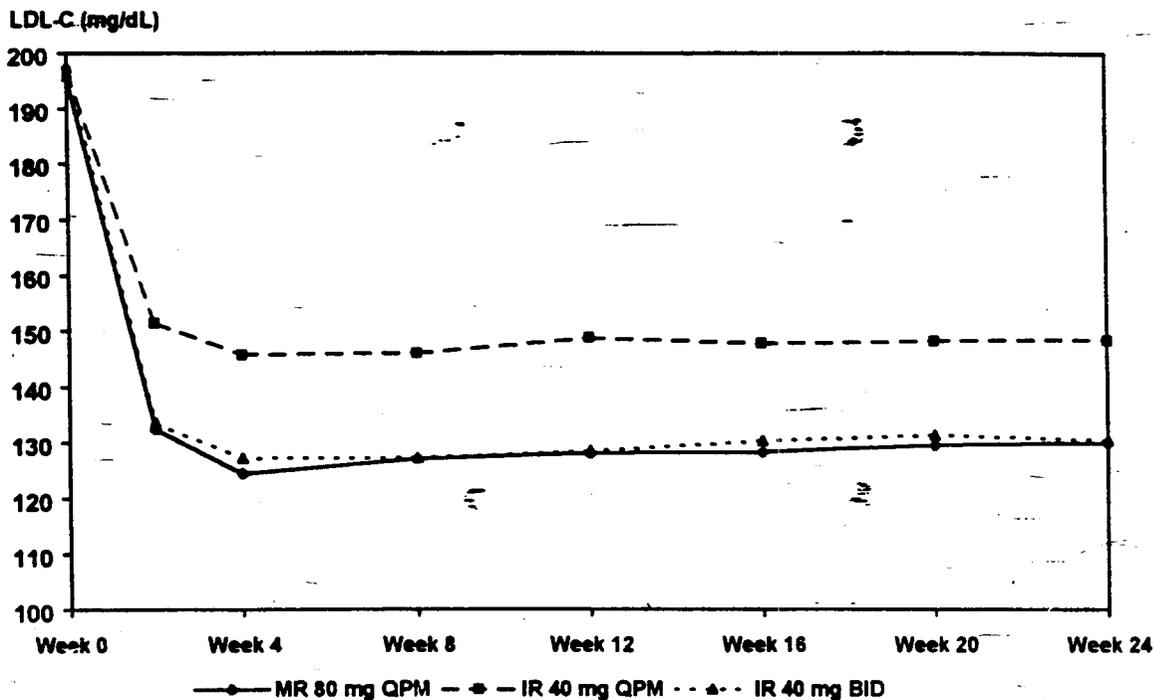
Gender/Age (yrs)	Fluvastatin MR 80mg QPM N/Mean % reductions	Fluvastatin IR 40 mg QPM N/Mean % reductions	Fluvastatin IR 40 mg BID N/Mean % reductions
Males <65	311/29.7	188/20.8	127/30.4
Males ≥65	91/34.0	38/28.4	29/36.9
Females >50	80/32.1	52/21.4	28/26.9
Females <50	367/33.8	222/26.0	141/34.4
Females <65	305/33.4	178/23.8	130/33.7
Females ≥65	142/33.8	96/27.5	39/31.3

According to the sponsor, "For the 6 gender and age group categories, the mean percent reductions in LDL-C were generally similar within each category for the fluvastatin MR 80 mg QPM and fluvastatin IR 40 mg BID groups. While the reductions were considerably less in the fluvastatin IR 40 mg QPM group, the reductions in LDL-C were similar within each category." The data were re-analyzed by J. Todd Sahlroot, Ph.D., Mathematical Statistician, to compare treatment differences in LDL-C reduction (MR 80 mg minus IR 40 mg QPM) for age and gender:

	95% C.I. for treatment difference	Point estimate
Age <65 years	(-11.2%----- -7.5%)	-9.3%
≥65 years	(-9.1%----- -3.1%)	-6.1%
Sex Male	(-11.0%----- -6.4%)	-8.7%
Female	(-10.5%----- -6.3%)	-8.4%
Interaction between age and treatment		P=0.13
Interaction between sex and treatment		P=0.71

When patients were administered MR 80 mg QPM instead of the IR 40 mg QPM, the increase in LDL-C reduction did not demonstrate any difference in terms of age or gender. Furthermore, there was no interaction between age and treatment or between gender and treatment.

2. LDL-C reduction by race will not be presented because Caucasian comprised 91.0%, 91.9% and 92.1% of the study patients in the Fluvastatin MR 80 mg QPM, Fluvastatin IR 40 mg QPM and Fluvastatin IR 40 mg BID treatment groups respectively. Therefore, efficacy comparison by racial subgroups is of questionable value.
3. Mean LDL-C reduction by week (all randomized patients) is depicted by the following figure as provided by the sponsor:



Mean LDL-C reduction was seen by Week 2, reaching a maximum by Week 4 and persisted until the Endpoint (Week 24).

4. LDL-C reductions from Baseline to Endpoint by phenotype are shown below:

Phenotype	Fluvastatin MR 80mg QPM N/Mean % reductions	Fluvastatin IR 40 mg QPM N/Mean % reductions	Fluvastatin IR 40 mg BID N/Mean % reductions
Type IIa (TG<200)	580/32.6	363/24.7	229/33.5
Type IIb (TG≥200)	269/31.2	137/21.2	96/29.8

The number of patients with IIa were more than 50% greater than Type IIb. However, there were sufficient number of patients, 269, to make the comparison meaningful. No clinically significant differences were observed between Types IIa and IIb.

Between treatment comparisons of LS means (LSM) are shown below:

Comparison	LSM diff. (SE)	95% CI	p-value for superiority	p-value for non-inferiority
80mg MR QPM vs 40mg IR QPM	-8.4 (0.81)	{-10.0, -6.8}	<0.001	---
80mg MR QPM vs. 40mg IR BID	-0.6 (1.00)	{-2.6, 1.4}	0.553	<0.001

At the Endpoint, the fluvastatin MR 80mg QPM group had an 8.4% (with 95% CI of 6.8 to 10.0 %) greater mean percent reduction in LDL-C than the fluvastatin IR 40mg

QPM group ($p < 0.001$). These results indicate that doubling the dose of fluvastatin reduced LDL-C by at least an additional 6% over a 24-week treatment period. The least square mean percent reduction in LDL-C at Endpoint for fluvastatin MR 80mg QPM was therapeutically equivalent (with 95% CI of -0.9 to 1.4%) to that of for fluvastatin IR 40mg BID treatment group ($p < 0.001$ for non-inferiority).

B. Secondary Efficacy Parameters: The secondary efficacy parameters included percent mean changes in total-C, apolipoprotein B, apolipoprotein A1, LDL:HDL ratio and percent median changes in HDL-C and TG.

1. HDL-C: Least squares mean (SE) percent change from Baseline to Endpoint (all randomized patients):

Treatment group	N	LS mean change from baseline (SE)
Fluvastatin MR 80mg QPM	849	8.3% (0.47)
Fluvastatin IR 40mg QPM	500	5.6% (0.59)
Fluvastatin IR 40mg BID	325	6.6% (0.77)

Between treatment comparisons of LS means (LSM) are shown below:

Comparison	LSM diff. (SE)	95% CI	p-value for superiority	p-value for non-inferiority
80mg MR QPM vs 40mg IR QPM	2.7 (0.75)	{ 1.2, 4.2 }	<0.001	---
80mg-MR QPM vs. 40mg IR QPM	1.7 (0.93)	{ -0.1, 3.5 }	0.062	<0.001

At Endpoint, the fluvastatin MR 80mg QPM-treated group showed non-inferiority to IR 40mg BID treatment group. The MR 80mg QPM group had a least-square mean percent increase in HDL-C which was 2.7% greater than that for the fluvastatin IR 40mg QPM treatment group. This was statistically significant ($p < 0.001$) according to the Sponsor. This is somewhat surprising because in the individual studies, only Study XUO-F353 ($n=139$ for MR 80mg QPM) demonstrated statistically significant difference in HDL-C between the treatment groups ($p < 0.05$). The two other studies XUO-F302 with $n=341$ and XUO-F351 with $n=369$ demonstrated no statistically significant difference between the treatment groups. The baseline lipid values for all studies were similar, particularly with regard to baseline HDL-C levels. The reason(s) for the different HDL-C efficacy results are not obvious. At any rate, the clinical significance of increasing HDL-C is yet to be determined.

Since HDL-C is not a normally distributed function, percentiles percent change from baseline maybe more informative:

Treatment group	N	Baseline mean	Percentile %-change
Fluvastatin MR 80mg QPM	849	51.8	
25 th percentile			0.0
Median			7.0
75 th percentile			15.0
Fluvastatin IR 40mg QPM	500	51.9	
25 th percentile			-1.1
Median			5.0
75 th percentile			12.9
Fluvastatin IR 40mg BID	325	51.0	
25 th percentile			-1.8
Median			6.0
75 th percentile			13.3

Although the median HDL-C increase for the MR 80mg QPM group was greater than that of IR 40mg QPM group, the graphs of cumulative distribution function show great overlap.

Mean percent changes in HDL-C from Baseline to Endpoint by HDL-C baseline value and phenotype is next examined:

Phenotype	HDL-C Level	Fluva. MR 80mg QPM; n/Mean % increase	Fluva. IR 40mg QPM; n/Mean % increase	Fluva. IR 40mg BID N/Mean % increase
Type IIa (TG<200)	<35	13/12.0	8/10.5	7/6.4
	≥35	567/6.0	355/5.1	222/5.4
Type IIb (TG≥200)	<35	22/15.9	17/9.4	6/6.2
	≥35	247/13.0	120/6.6	90/9.0

The sample sizes among the treatments within Types IIa and IIb (<35 mg/dL HDL-C) subgroups were very small. No meaningful conclusions regarding treatment differences can be made. For HDL-C ≥35 mg/dL subgroup, MR 80mg QPM group appeared to have greater increases than IR 40mg QPM or BID groups. The statistical and clinical significance of these differences are unknown.

3. Total-C: Mean percent reductions in total-C from Baseline to Endpoint among the 3 treatment groups are given below for all randomized patients:

Fluva. MR 80mg QPM; n/Mean % reduction	Fluva. IR 40mg QPM; n/Mean % reduction	Fluva. IR 40mg BID n/Mean % reduction
849/22.9	500/16.9	325/23.4

Mean percent reductions for fluvastatin MR 80mg QPM and fluvastatin IR mg BID were equivalent and 6% greater than those in patients treated with fluvastatin IR 40mg QPM.

4. TG: Mean percent reductions in TG from Baseline to Endpoint among the 3 treatment groups are depicted below:

Fluva. MR 80mg QPM; n/Mean % reduction	Fluva. IR 40mg QPM; n/Mean % reduction	Fluva. IR 40mg BID n/Mean % reduction
849/13.5	500/9.3	333225/13.7

At Endpoint, the fluvastatin MR 80mg QPM group and IR 40mg BID group had equivalent mean percent reductions in TG which was 4.0% greater than that for the fluvastatin IR 40mg QPM treatment group. The statistical and clinical significance of these differences is unknown.

Since TG is not a normally distributed function and shows large spontaneous fluctuations, percentiles percent change from baseline maybe more informative:

MR 80mg QPM	Median, 25 th , and 75 th Percentiles Percent change from Baseline ITT population		
	25 th	Median	75 th
Endpoint (N=849)	-32	-19	-1

The median increase for MR 80mg QPM was -19%. No statistical analysis was performed vs. IR 40mg QPM group, and the clinical significance of this finding is unknown.

Subgroup analysis by baseline TG values (baseline TG <200 mg/dL and >200 mg/dL) is shown below:

	Median, 25 th , and 75 th Percentiles of Percent change From Baseline: ITT population		
	25 th	Median	75 th
Type IIa (TG <200 mg/dL)			
Fluvastatin MR 80mg QPM	-29	-15	+ 4
Fluvastatin IR 40mg QPM	-26	-10	+ 8
Fluvastatin IR 40mg BID	-28	-15	+ 3
Type IIb (TG >200 mg/dL)			
Fluvastatin MR 80mg QPM	-38	-25	-10
Fluvastatin IR 40mg QPM	-34	-18	- 5
Fluvastatin IR 40mg BID	-38	-28	-11

The above results indicate that MR 80mg QPM treatment resulted in a greater percent decrease than IR 40mg QPM group in both Type IIa (TG<200) and Type IIb (TG>200). Furthermore, the percent decrease was generally greater in patients with baseline TG \geq 200 mg/dL. The statistical and clinical significance of these findings is unknown.

5. Apo B: Mean percent reductions in apolipoprotein B from Baseline to Endpoint by phenotype (all randomized patients) are shown below:

Phenotype	Fluva. MR 80mg QPM; n/Mean % reduction	Fluva. IR 40mg QPM; n/Mean % reduction	Fluva. IR 40mg BID N/Mean % reduction
Type IIa (TG<200)	557/24.7	347/18.4	214/25.4
Type IIb (TG>200)	261/23.8	130/16.1	88/22.3

The mean percent reductions in the MR 80mg QPM and IR 40mg BID groups were overall equivalent for both phenotype subgroups. They were greater than those for patients receiving IR 40mg QPM.

C. Reviewer's Conclusion and Evaluation:

- In the intent-to-treat integrated primary efficacy analysis, fluvastatin MR 80mg QPM reduced LDL-C by a least-squares mean at Endpoint of 32.2% compared to 23.8% with fluvastatin IR 40mg QPM. These results established the superiority of MR 80mg over IR 40mg QPM. Most of the LDL-C lowering was achieved after 2 weeks of treatment, with maximum reduction obtained after 4 weeks. This effect was maintained over the remaining 20 weeks of treatment. The MR 80mg QPM was effective in reducing LDL-C in all subgroups of patients by gender, age, baseline LDL-C levels and phenotype (Type IIa and IIb).
- Studies XUO-F302 and XUO-F353 were also designed to assess the non-inferiority in lowering LDL-C between MR 80mg QPM and IR 40mg BID. The least-squares mean decrease for IR 40mg BID was 31.6% at Endpoint; the least-squares mean difference was -0.6 (95% confidence intervals -2.5, 1.4). These results established the non-inferiority of MR 80mg compared to IR 40mg BID.
- Statistically significant differences from Baseline to Endpoint between MR 80mg QPM and IR 40mg QPM groups were also demonstrated in total-cholesterol, apolipoprotein B and LDL:HDL ratio. Only a trend for greater reductions in TG and greater increases in HDL-C and apolipoprotein A1 were observed. For further discussion of the HDL-C results, please see Statistical Consult Review.

Overall Conclusions and Recommendations:

- This NDA was submitted to register an 80mg modified release (MR) once a day dosage of fluvastatin. The main data consisted of 3 pivotal Phase III studies involving 1680 patients with primary hypercholesterolemia randomized to 3 treatment groups (MR 80mg QPM, IR 40mg QPM and IR 40mg BID) of 24 weeks in

- duration. The primary objective was to demonstrate therapeutic superiority of MR 80mg QPM treatment over IR 40mg QPM treatment.
2. With respect to primary efficacy parameter, MR 80mg QPM was superior than IR 40mg QPM in reducing LDL-C by >6% ($p < 0.001$) in both Type IIa and IIb patients with hyperlipoproteinemia. With respect to secondary efficacy parameters, MR 80mg QPM treatment also resulted in statistically significantly greater reductions in total-C, apolipoprotein B compared to treatment with IR 40mg QPM. Only a trend for greater reduction in TG and greater increases in HDL-C and Apolipoprotein A1 were demonstrated.
 3. With respect to safety, no new unexpected adverse events were reported. The incidence of AST/ALT elevations was similar in the 2 treatment groups with MR 80mg QPM and IR 40mg QPM. Furthermore, the incidence rates were comparable to other marketed statins. No patient treated with MR 80mg QPM developed CK>10xULN and no cases of rhabdomyolysis were reported.
 4. This NDA is approvable.

Review of Financial Disclosure Forms:

The following financial disclosure information had been submitted:

1. Form FDA 3454 (3/99). The sponsor certifies that Novartis has not entered into any of the following financial arrangements with the clinical investigators named in the lists included in the NDA:
 - A. Outcome payments (that is, payment dependent on outcome of the study).
 - B. Proprietary interests (e.g. patents/trademark/copyright/licensing agreement in the product).
 - C. Equity interest (e.g. stock ownership/stock options),
 - D. Significant payments of other sorts: Only two investigators, the principal investigator and sub-investigator in Study XUO-F351-E-00 (at Center 26) had received grant money from Novartis. This study randomized 555 patients in 30 centers. This unlikely that these two investigators had significant impact on the outcome of the entire Phase III studies of 1692 patients or the 849 patients randomized to Fluvastatin MR 80 mg WQPM.
2. List of investigators from who completed financial disclosure forms was received.
3. The sponsor certifies that all clinical investigators participating in and contributing data to the pivotal studies were requested and did provide to Novartis the requisite financial disclosure information.

Comments:

The above financial disclosure information was reviewed and there is no evidence to call into question the overall integrity of the data submitted.

21 pages redacted from this section of
the approval package consisted of draft labeling

SAFETY UPDATE REVIEW

Refer to Medical Officer Review