CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740

MEDICAL REVIEW(S)

June 4,1997
Division Director's Memorandum
To: the File NDA 20-740 Baycol(cerivastatin) Tablets
From: Solomon Sobel M.D., Director, Division of Metabolic and Endocrinologic Drug Products
Subject: Approval of NDA

This is an entirely synthetic entantiomerically pure inhibitor of 3 HMG CoA reductase

Tablets contain 0.2 or 0.3 milligrams of cerivastatin sodium.

The drug in addition to its effect on lowering LDL cholesterol, also lowers triglycerides and raises HDL cholesterol. The latter effects do not appear as indications.
There is no constant effect on Lp(a) concentrations.

The administration of cerivastatin with the evening meal did not significantly alter AUC or Cmax compared to dosing the drug 4 hours after the evening meal.
In the labeling , the results of a 24 week randomized, double-blind, placebo-controlled study in 695 patients was done in the United States.
At eight weeks, for those treated with cerivastatin 0.2mg daily there was a 25.0% reduction in LDL cholesterol; for those treated with 0.3mg daily there was a 29.4% reduction.
The respective changes for HDL were increases of 8.8% and 9.7%; for triglycerides there were reductions of 12.8% and 12.0%.
(Dr.Orloff and I will discuss the inclusion of the 24 endpoint data)

The safety profile for cerivastatin is good and is not different from the other statin drugs.

Conclusion: The Division recommends approval of this NDA.

/Solomon Sobel M.D.

CC: Orig. NDA 20-740
HFD-510/div. file
HFD-510/MSimoneau/SSobel

Medical team leader's comments on NDA
NDA # 20-740
NDA submission date: 6-26-96

Drug name: Cerivastatin sodium
Proposed trade name: BAYCOL

Sponsor: Bayer, West Haven, CT

Pharmacologic category: HMG-CoA reductase inhibitor
Proposed indication: treatment of hypercholesterolemia

Dosage forms: 50, 100, 200, 300 micrograms, oral

Related drugs: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin

The team leader was also the primary medical reviewer for this NDA. These comments are largely those in the Summary and Conclusions section of the NDA review.

Cerivastatin sodium is a purely synthetic HMG-CoA reductase inhibitor. It is administered as the salt of the hydroxy acid (active) form. It is a highly potent inhibitor of HMG-CoA reductase, approximately 100 times more potent than lovastatin.

This NDA contains data from extensive preclinical pharmacological and toxicologial investigations in animals, human pharmacokinetic studies, and human clinical studies of the safety and efficacy of chronic administration of cerivastatin. In addition, limited drug interaction studies and a study of the effect of cerivastatin on male adrenal and reproductive function have been undertaken and the results submitted. The results of a pharmacokinetic study of the interaction of cerivastatin with erythromycin were delivered to the Division on 5-29-97 for review with the intent of including them in the package insert for BAYCOL.

No novel toxic reactions were observed in animals. In studies in mice, the carcinogenic potential of cerivastatin in the liver was similar to that of other HMGRIs with respect to the relationship of the mouse systemic exposures to human exposures at the maximum recommended dose. Furthermore, what is likely more reflective of hepatic exposure in these animal studies, the dose per body weight, far exceeds the proposed human doses. The spectrum of adenomas and carcinomas in animals was the same as that seen with other HMGRIs.

The pharmacokinetic studies reveal good oral bioavailability (60% absolute.
and linear pharmacokinetics over a dosage range from 50 to 400 mcg. The elimination half-life No drug accumulation was observed with chronic once daily dosing.

The original proposed dosage range for cerivastatin was 50 to 300 mcg once daily in the evening. The absolute efficacy of the drug at these doses in LDL-C lowering is limited relative to other

marketed statins. Data from the pivotal efficacy studies showed mean LDL-C lowering in response to 300 mcg daily of approximately 30%. In addition to inducing the expected lesser effect on total-C that parallels the dose-related effect on LDL-C, cerivastatin, like the other members of the class, effected non-dose-related mean increases in HDL-C and mean reductions in TG in patients with primary hypercholesterolemia or mixed dyslipidemia (with elevations in VLDL). The mean reductions in TG were, at the higher doses of drug, statistically significantly different from placebo.

Cerivastatin was studied in FH heterozygotes but not in FH homozygotes.

The exposure to cerivastatin in controlled clinical trials in this development program was substantial, with nearly 3500 patients treated across the dosage range. The exposure to 300 mcg daily was greater than 550 patients for at least 6 months, ~250 patients for at least one year, ~100 patients for at least 2 years, and ~80 patients for 30 months. Fewer than 10% of patients studied in both the US and abroad were non-Caucasian. Multiple studies in Japan are ongoing. Women were well represented, constituting approximately 50% of the patients studied. Pediatric patients were not studied. Finally, in an 8-week study comparing cerivastatin 400 mcg to cerivastatin 300 mcg (~140 patients each) and to placebo (~70 patients), the doses of cerivastatin were equally well tolerated.

No unexpected adverse events attributed to cerivastatin were observed in the clinical trials. In general, the drug was very well tolerated. Few adverse events occurred more frequently among cerivastatin than placebo patients, and for those events, the rates among active control statin-treated patients were generally higher than among the cerivastatin patients. These included diarrhea, arthralgia, myalgia, sinusitis, and increased cough. There were no effects on adverse event rates of dose, gender, or age.

With regard to labeling, I have recommended that the efficacy data presented be based on analysis of data from the intent-to-treat populations in the interest of consistency with labeling of other lipid altering agents.

The other major addition to the proposed label is the inclusion in the Pregnancy section of information gleaned from the recently published followup of patients inadvertently exposed to lovastatin and simvastatin, for the most part in the early first trimester of pregnancy. This review found no increase in the incidence of fetal anomalies, miscarriages, or stillbirths relative to the expected rates in the general population. The use of HMGRIs in pregnancy is still contraindicated. This information is included in labeling to inform physicians and patients of recent data speaking to the risks to the fetus of inadvertent exposure to these agents *in utero*.

In recent days, the sponsor has proposed limiting marketing to the 200 and 300 mcg dosage forms, while still requesting approval of the 50 and 100 mcg dosage forms. This is a marketing decision apparently based on the limited potency of the lower dosage forms and the knowledge that across the statin class, the lower doses are not widely used. In considering this proposal, it is germane that in the U.S. pivotal trial, the difference between the 200 and 300 mcg groups in mean percent LDL-C lowering from baseline to endpoint was statistically significant. In addition, no

dose-related adverse reactions or toxicities were evident in the analysis of the safety of cerivastatin that would mandate against a starting dose of 200 mcg. Therefore, with appropriate changes in labeling, this approach is acceptable. Finally, I would recommend leaving table 1 of the label as is (including the 50 and 100 mcg doses) in order to convey the clear dose-response to cerivastatin in lowering total and LDL-C.

Conclusions

Cerivastatin sodium, a new HMG-CoA reductase inhibitor appears safe and effective as proposed for use in patients with primary hypercholesterolemia and mixed dyslipidemia at doses from 50 to 300 mcg once daily. This conclusion is based on data from extensive preclinical studies and on safety and efficacy data from a large exposure in human clinical trials, up to 30 months at the highest dose (300 mcg) proposed for marketing.

Recommendations

Based on the materials reviewed and pending agreement on final labeling, BAYCOL (cerivastatin sodium) tablets should be approved for marketing as proposed in NDA 20-740.

David G. Orloff, M.D.
Medical Officer/Team Leader
DMEDP/CDER/FDA

concur: Dr. Sobel

5-29-97

cc:
NDA Arch 20-740
HFD-510

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ON ORIGINAL

Medical Officer's review of NDA
NDA # 20-740
NDA submission date: 6-26-96
review completed: 5-29-97

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Medical Reviewer: David G. Orloff, M.D.
Statistical input: Joy Mele, M.S.

This review consists of 101 pages

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Section 1 Materials reviewed:
Volumes 1.1-1.2, 1.230-1.580, 1.675-1.676, 4-month safety update, male adrenal and reproductive function study (D94-021), final safety update submitted 5-16-97

NDA 20-740 was submitted in paper format as well as in a computer-based format. Only the overall summaries (safety, efficacy) and the individual study summaries were available to this reviewer in the CANDA. The summary tables were in paper format only. The focus of this review was on the clinical data sections. Cursory review of specific portions of the chemistry, pharmacology, and pharmacokinetics sections was also undertaken. Narratives for deaths, discontinuations due to adverse events, and clinically important ALT/AST and CPK abnormalities were also reviewed.

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Section 2
Background
Introduction

HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. It catalyzes the conversion of HMG-CoA to mevalonate in the pathway to cholesterol, dolichol, and ubiquinone (coenzyme Q). The pharmacologic class of drugs that act as inhibitors of this enzyme has become the mainstay of therapy for primary hypercholesterolemia and mixed dyslipidemia, and several marketed drugs have been proven effective in slowing progression of atherosclerosis as well as in reducing rates of fatal and non-fatal atherosclerosis-related events in populations at risk.

Chronic inhibition of this enzyme in the liver effects reductions in intrahepatic cholesterol pools with a resultant increase in the expression of cell-surface LDL-receptors. The augmented binding and endocytosis of LDL particles mediated by these new receptors accelerates the clearance of LDL-C from the circulation, and a reduced steady state level of cholesterol and LDL-C in the plasma is reached. The HMG-CoA reductase inhibitors (HMGRIs) or statins, also tend to lower VLDL concentrations, both by increasing clearance via LDL (B,E)-receptors and by affecting the rate of synthesis of cholesterol and thus the assembly and secretion of VLDL. This results in a reduction in fasting plasma triglyceride levels.

Cerivastatin is a purely synthetic, extremely potent inhibitor of HMG-CoA reductase. The sixth member of this class of highly effective cholesterol-lowering agents proposed for marketing, it possesses a unique structure and is approximately 100 times more potent as an inhibitor of its cognate enzyme than is lovastatin.

Cerivastatin, like fluvastatin, pravastatin, and atorvastatin, is administered as the salt of the active, hydroxy acid form. Lovastatin and simvastatin, administered as closed ring lactones, must be hydrolyzed in the liver to their active hydroxy acid forms.

Animal studies suggest that cerivastatin, like the other HMGRIs, is readily absorbed via the oral route, undergoes extensive first-pass hepatic extraction, is concentrated in the liver, and is a potent inhibitor of hepatic cholesterol biosynthesis. Furthermore, like its predecessors, cerivastatin lowers plasma cholesterol and LDL in several animal models including beagle dogs and hypercholesterolemic rabbits.

The toxicological profile of cerivastatin in animals is similar to those of the other statins, with no novel toxic reactions observed (see toxicology summary).

The overall planning of the development of cerivastatin, and thus of the review of this NDA, was clearly impacted by the extensive knowledge of the preclinical pharmacology and toxicology, as well as of the clinical safety and efficacy, of the earlier marketed statins. The large body of work on the biochemistry of cholesterol metabolism, the mechanism of action of the HMGRIs, and the large and increasing clinical experience demonstrating the safety and efficacy of these agents

influence the approach to the data submitted.

With regard to efficacy, this drug, like other members of the class, clearly works to lower total and LDL-C in patients with hypercholesterolemia. The remarkable fact of this treatment approach is that it works in virtually all patients with heterozygous familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia. In patients with heterozygous FH, HMGRIs produce less dramatic effects, as a rule, presumably because of a decreased capacity to up-regulate expression of functional LDL-receptors. For the same reason, only more markedly so, patients with homozygous FH respond even less well to HMGRIs. Indeed, until fairly recently, these agents were felt not to work in these patients, at least not at doses that would otherwise be tolerated from the standpoint of hepatic and other systemic toxicities. Overall, though, in appropriately chosen individuals and populations, each of the statins demonstrates consistent dose-dependent effects on plasma lipids. In short, HMG-CoA reductase inhibition is a highly effective means of lowering plasma cholesterol in a variety of patients.

The review of the efficacy of cerivastatin, therefore, does not include summaries of all of the lipid altering data contained in the NDA. The pivotal studies have been reviewed, as some of these results have been incorporated into proposed labeling. In addition, some long-term data have been reviewed in order to document the time course and durability of the response to the drug, again a well-defined characteristic of the class. The dose-scheduling study has been reviewed in brief simply to establish the appropriate timing of dosing of the drug for purposes of labeling.

Some of the sponsor's exploratory analyses in pooled datasets have been included, among them the effects of age, gender, and lipoprotein phenotype on the response to drug. Suffice it to say that the distinguishing feature of the cerivastatin efficacy data is the limited absolute potency in cholesterol lowering of the dosage range proposed for marketing.

The remainder of the completed studies are not reviewed here from the standpoint of efficacy, but data from the patients exposed therein were included in the overall review of safety.

With regard to safety, again the sponsor's overall approach and the approach of this reviewer took into account the known safety issues associated with this class of drugs. Side effects of the class include gastrointestinal disturbances as diarrhea, constipation, dyspepsia, nausea, and flatulence, rare CNS effects including insomnia, and effects more clearly attributable to drug in the liver and skeletal muscle. Studies in dogs have shown effects on testicular function and cataract formation, neither organ being adversely affected in humans.

Thus, the safety review will include an assessment of the overall rate and spectrum of adverse effects as well as the frequency distribution for individual adverse events as is relevant. A summary of the data regarding liver function abnormalities and creatine kinase elevations will also be included. Ophthalmologic data will be briefly summarized, and the study on male reproductive function will be reviewed.

The sponsor has limited the dose range for the time being to 300 mcg daily, which appears very well tolerated. Although it does not appear to be an issue for the NDA, the extreme potency of cerivastatin (100-fold that of lovastatin as an inhibitor of HMG-CoA) may impact on its therapeutic index. That is, depending on the efficiency of metabolism and clearance by the liver, it is conceivable that even at doses not effecting great reductions in LDL-C, sufficient systemic exposure may result to limit therapy with this drug. Pharmacokinetic data at higher doses will shed light on this issue. Finally, the sponsor has not yet presented data on interactions of cerivastatin with drugs that inhibit CYP3A4, the microsomal enzyme responsible for metabolism of most of the other statins. For the other members of the class of HMGRIs so studied, co-administration with fibrates, cyclosporine, erythromycin, and itraconazole can increase systemic levels of the statins, presumably the cause of the occasional case of rhabomyolysis seen in such situations. Whether similar interactions occur with cerivastatin is not, at this point, known.

Indications

The proposed indication for Cerivastatin is "as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types II and II b), when the response to dietaty restriction of staturated fata and cholesterol and other nonpharmacological measures alone has been inadequate."

Administrative history

Highlights of meetings and communications between the sponsor and DMEDP

The cerivastatin IND was submitted to the FDA on March 19, 1991. The clinical program designed was consistent with the draft Guidelines for the Clinical Evaluation of Lipid Altering Agents in Adults and Children. In addition, the FDA requested an adrenal and reproductive study designed to assess both basal and reserve hormonal production and human plasma levels on a subset of patients in Phase II and Phase III of development.

On November 24, 1992, a conference call was held with the FDA to discuss long term dosing of CER in humans. Bayer proposed a study (D91-031 [0124]) which would consist of an initial 6 - 10 week placebo run-in, followed by patient randomization into a placebo-controlled double blind 24 week treatment regimen. This regimen would then be followed by an eighteen month extension.

On December 30, 1992, the FDA contacted Bayer to advise that the 6 month study (D91-031 [0124]) could begin the dietary lead in.

On February 4, 1993, Bayer was granted approval by FDA to begin the 24 week clinical trial (D91-031 [0124]).

On March 30, 1995, a video conference was held to discuss the content and format of the clinical sections of the CER NDA. The FDA found the proposed data format to be acceptable, but

commented on the extent of 300 µg long term exposure data. It was also determined that the male reproductive function study must be submitted within six months after filing the NDA and that Japanese data available at the time of submission was acceptable. The FDA requested that Bayer:

1. Determine the risk associated with limited 300 µg 2 year exposure data and evaluate the impact of a possible approval of 200 µg as the highest dose.
2. Determine an acceptable NDA filing date based on (1) and also the availability of the male hormone study report (D94-021 [0152]).

On August 29, 1995, a pre-NDA meeting was held at the agency. The following issues were agreed upon:

- Methods Validation Package:
  1. will be the compounds which are actually characterized by the FDA laboratories. Full characterization and stability information must be available on the BAY w 8877 as well as the BAY w 6228 BAY w 6228 and BAY w 8877 will also be provided to the FDA labs for analysis.
  2. One year stability data from the manufacturing site in is necessary for NCE approval. Six, nine and twelve month stability data were promised to the FDA.

- Toxicology Section:
  1. Further characterization of the M23 metabolite since human data determined that 50 % of the CER activity is attributed to M23. Twenty five percent of the lipid lowering activity is from M23, based on human plasma levels.
  2. Dominant lethal assay of M23 in mice is to be conducted.
  3. Human in vivo PK data on M23 and M24 must be provided to the FDA.
  4. M23 toxicology protocols are to be submitted prior to initiating the studies.

- Human Clinical Pharmacology Section:
  1. Due to the fact that all tablet strengths have nearly the same active/excipient ratio, the recommendation in the labeling would be for use of a single, distinct tablet for the dosing regimen.
  2. The FDA expressed the possible need for bioequivalence of all tablet strengths.
  3. There is an ongoing dose proportionality study (0154) which will be completed and included in the NDA submission.
  4. Further tests to characterize the PK of the 50 µg dose are to be conducted.

- Clinical Section:
  1. Approvability of the 300 µg dose would be dependent upon the safety profile from the 2 year study.

2. The cut-off date for reporting of discontinuations due to adverse events, serious/unexpected adverse events, and deaths for ongoing studies would be 12/31/95.
3. CRFs and narratives to be provided for discontinuations due to adverse events, deaths, and serious/unexpected events which were reported to the FDA as 3 or 10 day reports.
4. Narratives only to be provided for serious/unexpected reports which were reported to the FDA as periodic reports.
5. The safety and efficacy study of CER 400 µg (0149) to be submitted in the 4 month safety update. (Note: Although this study was not expected until the 4 month safety update, it is included in the original NDA submission.)
6. The male reproductive study (D94-021 [0152]) to be submitted 6 months after submission.
7. All CER publications will be submitted as well as a review of selected relevant publications on the class of HMG-CoA reductase inhibitors.

- Submission:
  1. Submit a full paper copy of the NDA and, on a limited basis, provide electronic data and word processing files as they would facilitate review. The division to grant a waiver of paper CRFs if an electronic submission is done.
  2. The proposed clinical package is thought to be "fileable". Four hundred microgram doses and some exposure beyond 2 years would increase FDA comfort with the 300 µg dose.

Proposed directions for use: dose, timing, concomitant meds, renal insufficiency
The recommended starting dose is 50 to 100 mcg daily. Monitoring of response and dose adjustments are recommended at 4 weeks after initiation of therapy or change in dose. The drug is to be taken once daily in the evening, with or without food.

The label describes the additive effects of bile acid sequestrants and cerivastatin and recommends waiting 2 hours after a dose of resin before taking cerivastatin.

The label contains warnings regarding comcomitant use of cerivastatin with immunosuppressive drugs, gemfibrozil, erythromycin, and niacin at lipid-lowering doses. No mention of the potential for an interaction with itraconazole is made.

The label recommends that for patients with advanced renal disease, patients be monitored carefully, though the nature of the monitoring is not described.

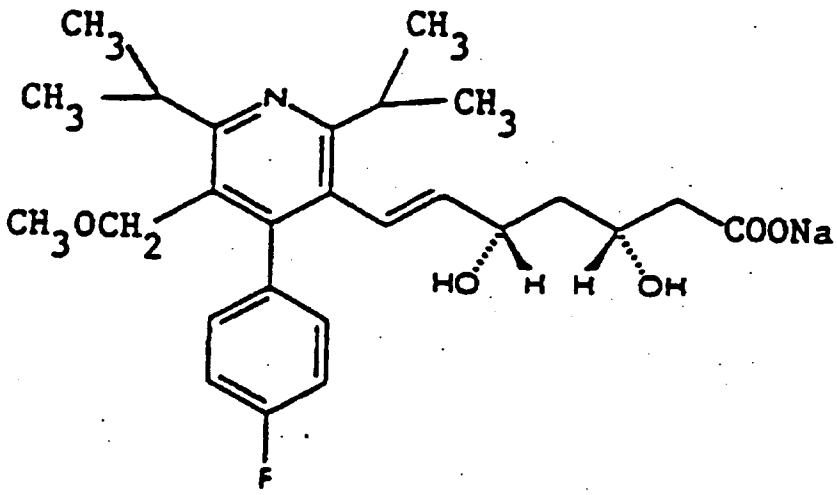
Foreign marketing
Cerivastatin is not marketed in any country.

Section 3
Chemistry

For comprehensive information, see chemist's review of this NDA.

Cerivastatin sodium is sodium [S-[R*,S*-(E)]]-7-[4-(4-fluorophenyl)-5-methoxymethyl)-2,6bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-6-heptenoate. The Chemical Abstracts registry number is 143201-11-0. Cerivastatin sodium has the Bayer AG code number Bay w 6228.

The chemical structure of cerivastatin is shown below:



Cerivastatin sodium is a white to off-white hygroscopic amorphous powder that is soluble in water, methanol, ethanol and very slightly soluble in acetone.

Section 4
Preclinical pharmacology and toxicology

For comprehensive review, see pharmacologist review of the NDA. This brief section is excerpted from the sponsor's summary and is included here for the purposes of providing additional relevant background for the evaluation of the safety and efficacy of cerivastatin in humans.

Animal pharmacology
Cerivastatin significantly and dose-dependently decreased serum cholesterol and LDL levels when administered subchronically in beagle dogs and New Zealand white hypercholesterolemic rabbits.

The ED_{50} for inhibition of hepatic cholesterol synthesis in rats was approximately 100 times lower than that of lovastatin. The duration of the inhibitory action of cerivastatin on hepatic cholesterol synthesis following a single oral dose in rats was shown to be at least eight hours, exceeding that of lovastatin in a head-to-head study. This is felt due to to activity of cerivastatin metabolites as inhibitors of HMG-CoA reductase.

Cerivastatin was also shown to inhibit cholesterol synthesis in adrenal glands in rats as potently as in the liver (ED_{50} = 2 μg/kg body weight). On the other hand, cerivastatin failed to produce a dose-dependent inhibition of cholesterol level in the small intestine or testicles.

In vitro testing of cerivastatin using membrane-bound HMG-CoA reductase extracted from rat liver established a K_i value of 1.3×10^{-9}. By comparison, the K_i for lovastatin was 1.5×10^{-7} and for the natural substrate HMG-CoA, the K_i was 2.3×10^{-5}.

The activity of cerivastatin appears to be stereo-specific; the inactive (-) enantiomer has no more than 1% of the potency of cerivastatin.

Cerivastatin is demethylated and hydroxylated in man. When administered intravenously to rats, two major metabolites (M23 and M24) strongly and dose-dependently inhibit the conversion of acetate into cholesterol in the liver. This suggests that the pharmacodynamic activity of cerivastatin may be substantially longer than its pharmacokinetics would suggest.

In extensive testing in mice, rats, and guinea-pigs, cerivastatin administered orally or intravenously was found to have no adverse effects upon cardiovascular, gastrointestinal, renal, metabolic, hematological, or pulmonary parameters. In the CNS-safety studies, however, diarrhea and various CNS-related effects including increases in salivation, a slight elevation of body temperature, restlessness, rearing, and enhanced hexobarbital-induced anesthesia were observed when cerivastatin was administered intravenously at 30 μg/kg or orally at 300 μg/kg.

Like cerivastatin itself, the hydroxylated metabolite (M23) also caused an increase in the cholinergic-like responses in the CNS-safety studies in rats: increased restlessness and activity,

salivation, and diarrhea. These effects were dose-dependent and appeared at dosages of 100 µg/kg i.v. and above. In addition, in rats M23 caused a decrease in sodium excretion at 30 µg/kg i.v., a decrease in urinary volume at 100 µg/kg i.v., and an increase in blood glucose and decrease in triglyceride at 300 µg/kg intravenous. In guinea pigs, M23 at 30 µg/kg and above significantly enhanced the sensitivity of the airways to histamine. The latter effects were not observed with similar dosages of cerivastatin.

Summary of Multidose Toxicity studies

Major target organs detected in rodent studies with cerivastatin after treatment for periods of up to six months were: liver (changes in liver enzymes, pleomorphic hepatocytes, karyomegaly and cytomegaly, hepatocellular foci); skeletal musculature (degeneration / necrosis of muscle fibers); and forestomach (epithelial hyperkeratosis, in rats only).

Hyperkeratosis was not observed in other parts of the GI tract. In addition, since the human stomach has no counterpart to the forestomach in rodents, hyperkeratosis found in this organ in rats is considered to be of minor relevance for human safety assessment.

In the 13-week rat study, high doses of cerivastatin resulted in mortality, changes in the skeletal musculature, hyperkeratosis in the forestomach, and hepatic lesions. When mevalonate (MAL) was administered concurrently with cerivastatin, no deaths and no changes in the musculature occurred, and the hepatotoxic effects were ameliorated. The decrease in ubiquinone observed in heart muscle in rats treated with cerivastatin for six months could be prevented by the concurrent administration of MAL. With other statins, effects induced by inhibition of HMG-CoA reductase could also be suppressed or ameliorated by concomitant MAL. Lovastatin treated rats revealed a decrease in the ubiquinone levels in heart, liver, and blood. Therefore, adverse effects detected in the above-mentioned rodent studies with cerivastatin most likely may result from exaggeration of the pharmacological principle of the drug at high dose levels.

All the target organs and effects identified in rodent studies with cerivastatin are known from rodent studies performed with other statins

In non-rodents, target organs identified in subacute to subchronic studies with cerivastatin included the liver (changes in liver enzymes, parenchymal reaction), GI tract including gall bladder (erosions, bleeding), lymphatic system (edema, necrosis), skeletal musculature (degeneration, necrosis), eyes (cataracts, dog only), and kidney (degeneration in the proximal tubules, mini pig only).

In dogs, higher doses of cerivastatin resulted in a series of effects in different organs and mortality. When MAL was applied concurrently with cerivastatin (see 13-week dog study), the only findings consisted of elevated ALT and cataract formation. These results give strong evidence that the majority of adverse effects are likely to be the result of an exaggerated pharmacological activity of cerivastatin.

As with other statins, cataracts were only observed in dogs.

In addition to the findings observed in subacute and subchronic oral dog studies, chronic oral treatment of dogs with cerivastatin resulted in effects on the CNS and on the testicles. CNS effects at a dose of 0.1 mg/kg cerivastatin, a dose already lethal to dogs, consisted of multifocal CNS bleedings with fibrinoid degeneration of the vessel walls in the choroid plexus of the brain (one dog) and ciliary body of the eye. In the testicles, atrophy and vacuolization of the germinal epithelium, and spermatidic giant cells were observed. As with other statins, the incidence and grade of alterations in the testicles were poorly reproducible, and there was no clear dose-response relationship.

Hemorrhage was observed microscopically in dogs administered cerivastatin in lethal doses. Prolongation of the partial thromboplastin time noted at high dose levels in the 4-Week and in the chronic dog studies, is an indication for an influence of the treatment on the pathways in blood coagulation.

The kidney was found as an additional toxicological target for cerivastatin in a non-rodent species, the mini pig. The relevance of the degeneration of the proximal tubular epithelium seen for human risk assessment is unclear. The effect was observed at a high daily oral dose of 4 mg/kg that produced plasma concentrations corresponding to 228 times the human level (300 µg dose).

The studies in monkeys did not reveal any effect at daily oral doses of up to 0.1 mg/kg administered for 13 weeks or for 1 year. This dose corresponds to 5 times the human C_{max} at the 300 µg dose.

In conclusion, the target organs and effects found with cerivastatin in non-rodent studies in general are known from studies performed in non-rodents with other statins. Changes induced by the other statins included effects on the liver, CNS, GI tract including gall bladder, thymus, heart, kidney, and cataracts in dogs.

Carcinogenicity

In the 2-year carcinogenicity study in rats, there was no tumorigenicity up to and including a dose of 0.158 mg/kg/day cerivastatin, or 36 mg/kg/day lovastatin. The level of 0.158 mg/kg/day was the maximum tolerated dose of cerivastatin and resulted in a mean plasma concentration C_{max} of about 6 µg/l and an AUC of about 54 µg*h/l. These plasma concentrations are about 2 - 3 times the mean levels in humans taken the dose of 300 µg /day.

The carcinogenicity study conducted in mice with average daily doses of 0.4, 1.8, 9.1, or 55 mg/kg cerivastatin for 24 months revealed an increased incidence of hepatocellular adenomas in males and females, and of hepatocellular carcinomas in males from the 9.1 and 55 mg/kg dose groups.

The induction of tumors in carcinogenicity studies in rodents treated with HMG-CoA reductase

inhibitors is known from other statins. In contrast to other statins, intake of cerivastatin in the diet at very high doses induced only tumors in the liver.

Summary of other toxicological endpoints

No evidence of mutagenicity was observed in vitro with or without metabolic activation in the following assays: microbial mutagen tests (Ames Test) using mutant strains of S. typhimurium or E. coli, Chinese Hamster Ovary Forward Mutation Assay, Unscheduled DNA Synthesis in rat primary hepatocytes, chromosome aberrations in Chinese Hamster Ovary cells, and spindle inhibition in human lymphocytes. In addition, there was no evidence of mutagenicity in vivo in either a mouse Micronucleus Test, or in two mouse Dominant Lethal Tests.

In a combined male and female fertility study conducted in rats, cerivastatin had no adverse effects on fertility or reproductive performance at doses up to 0.1 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 1 - 2 times the mean plasma drug levels for humans receiving 300 µg cerivastatin/day. At a dose of 0.3 mg/kg/day (plasma C_{max} 4 - 5 times the human level), a marginal reduction in fetal weight, and delay in bone development was observed; the length of gestation was marginally prolonged, stillbirths were increased, and the survival rate up to day 4 postpartum was decreased.

Cerivastatin was not teratogenic and did not promote developmental toxicity in rats at oral doses up to 0.72 mg/kg, and in rabbits at oral doses of up to 0.75 mg/kg. These doses resulted in plasma levels (C_{max}) 6 - 7 times the human exposure (human dose 300 µg) for rats and 3 - 4 times the human exposure for rabbits.

In an oral peri-/postnatal toxicity study in rats, the only finding was early postpartum mortalility of two F1 litters at the highest dose administered. This dose corresponded to a multiple of about 3 times the plasma C_{max} in humans (300 µg daily dose).

Target organs in toxicological studies with cerivastatin and their safety range with respect to the human exposure

For humans, calculations are based on plasma levels of cerivastatin attained with the 300 µg dose in male volunteers. The free fraction of cerivastatin in human plasma is and 1.85% and 2.5% in dog and rat plasma, respectively.

Table 7 : Cerivastatin: Selected Toxicological Targets
NOAEL, Lowest Effect Level (LEL) and Multiples of
Total Plasma Concentration (C_{max}) to Humans

Target Organ Species	Dose mg/kg/day p.o.		Multiples of C_{max} to Humans **		Reference Toxicology
	NOAEL *	LEL	NOAEL	LEL	Study
Liver (Transaminases)					
Rat	0.105	0.21	1.5	1.7	*6,11*
Dog	0.01	0.025	1.7	6.3	*18, 22,23*
Monkey	> 0.1	-	> 5	-	*34*
Testicles					
Rat	> 5	-	> 571	-	*7*
Dog	< 0.008	0.008	< 1.4	1.4	*22,23*
Monkey	> 0.1	-	> 5	-	*34*
Musculature					
Rat	0.045	0.158	0.4	1.2	*13,14*
Dog	0.025	0.07	6.3	11	*22,23*
Monkey	> 0.1	-	> 5	-	*34*
CNS, GI tract (bleeding)					
Rat	> 5	-	> 571	-	*7*
Dog	0.07	0.1	11	23	*26,22,23*
Monkey	> 0.1	-	> 5	-	*34*
Lymphatic system (edema, necrosis)					
Rat	> 5	-	> 571	-	*7*
Dog	0.025	0.07	6.3	11	*26,22,23*
Monkey	> 0.1	-	> 5	-	*34*
Eyes (cataracts)					
Rat	> 5	-	> 571	-	*7*
Dog	0.07	0.1	11	23	*26,22,23*
Monkey	> 0.1	-	> 5	-	*34*

* : > indicates that the effect was not observed at the highest dose tested

** : based on free plasma concentrations of cerivastatin, multiples to humans are higher by a factor of 2.6 for dogs and by a factor of 3.6 for rats

From the data in the table above, in those organ systems for which an effect of cerivastatin was observed in animals, there appear to be comfortable safety margins with respect to human

exposures at 300 mcg/day, especially if the interspecies factors for the free fractions are taken into account.

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Section 5
Clinical data sources

Clinical development program

The CER clinical development consists of sixty-two studies performed both within and outside the United States. There are thirty four Phase I studies, four Phase II studies and three pivotal Phase III studies. The remaining twenty one studies consist of supportive and long term studies. The daily doses of CER used in these studies ranged from 20 μg to 400 μg. A total of 517 healthy volunteers have received cerivastatin in clinical pharmacology studies to date and, as of the last update in May 1997, and 3,448 patients received CER in clinical trials with a treatment duration from 1 day to 30 months.

The exposure in US and non-US clinical trials by dose and duration of therapy is summarized the tables below. These tables are also reproduced in the safety review (section 8).

Table 5.1
Number of CER-Treated Patients In Completed US Studies by Treatment Duration and Dose
(Patients Valid for Safety)

Dose	1 month	6 months	12 months	24 months	**30 months*‡** (CER 300μg)
CER 25μg qd	33	0	0	0	**0**
CER 50μg qd	182	141	109	98	**82**
CER 100μg qd	186	139	98	91	**77**
CER 100μg bid	89	0	0	0	**0**
CER 200μg qd†	467	242	205	**180**	**86**
CER 300μg qd	**210**	**168**	104	98	**82**
TOTAL CER	**1,167**	**690**	516	**467**	**327**

* This timepoint refers to total CER exposure duration. All patients in this column were switched from their respective CER dose to CER 300μg once daily from months 24 to 30.

‡ range: 814 to 983 days

† Patients treated with PLA in D91-031 (6 months) were treated with CER 200μg in X91-031 (18 months) and CER 300μg in Y91-031 (6 months). These patients are included in the CER 200μg 1, 6, 12 and 24 month exposure columns, however the last six months of the total two year exposure was exposure to CER 300μg.

The patients in the 50, 100, and 200 mcg rows enumerated in the last column and who were switched for the last 6 months of treatment to cerivastatin 300 mcg should be added to the

cerivastatin 300 mcg 6-months total, yielding a total of 413 patients exposed to cerivastatin 300 for 6 months.

The tables that follow summarize the clinical studies submitted in this NDA.

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Table 5.2
Number of CER-Treated Patients In Non-US Fixed-Dose Studies by Treatment Duration and Dose (Patients Valid for Safety)

Dose	1 month	3 months	12 months	24 months
CER 25µg qd†	359	292	217	78
CER 50µg qd	216	147	139	77
CER 100µg qd‡	**449**	**372**	**280**	95
CER 200µg qd	402	315	**290**	101
CER 300µg qd	327	164	**140**	0
CER 400µg qd	136	0	0	0
TOTAL CER	**1,889**	**1,290**	**1,066**	351

† Patients treated with PLA in Study 0120 (12 weeks) were treated with CER 25µg in X0120 (88 weeks). These patients are included in the CER 25µg 1, 3 and 12 month exposure columns.

‡ Patients treated with PLA in Study 0132 (16 weeks) were treated with CER 100µg in X0132 (36 weeks). These patients are included in the CER 100µg 1 and 3 month exposure columns.

Adequacy of the exposure

The known, mechanism-of-action-related adverse effects of the HMGRIs generally occur early in the course of therapy, within 6 to 12 weeks of initiation of treatment at a given dose. The exposure over the dosage range for durations of greater than three months is more than adequate to have detected effects on liver function and in the muscle occurring at rates comparable to or greater than are known to occur with other HMGRIs. With regard to exposure at the highest dose proposed for marketing, 300 mcg, the exposure was likewise adequate, with 140 patients treated for 12 months in non-US studies and 104 patients treated for 12 months in US studies. In

addition, the duration of exposure to 300 mcg daily was extended to 2 years and 30 months, in 98 and 82 patients, respectively.

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Table 1
US and Non-US Pivotal Studies

Region/ Study Number	Description	Doses*	Number of Patients: Randomized/ Valid for Efficacy/Completed	Lipid entry criteria	Age range (mean)	% M/F (% B/W/O)	Study Duration
US D91-031 (0124)	pivotal, dose-ranging; placebo-controlled; LOV comparison	CER 50µg CER 100µg CER 200µg CER 300µg LOV 40mg PLA	159/145/140 157/136/139 159/138/143 156/137/134 154/136/137 154/139/136	CLDL-C ≥ 160 TG ≤ 350	(57)	53/47 (5/93/2)	24 weeks
Non-US 0132	pivotal, dose-ranging; placebo-controlled; GEM comparison	CER 100µg CER 200µg CER 300µg GEM 600mg bid PLA	166/131/154 171/142/163 175/139/163 160/121/142 79/59/70	LDL-C ≥160 TG ≥ 190 and ≤ 500	(55)	55/45 (0/98/2)	16 weeks
Non-US 0120	pivotal, dose-ranging; placebo-controlled; SIMVA comparison	CER 25µg CER 50µg CER 100µg CER 200µg SIMVA 20mg PLA	196/153/179 194/146/177 195/156/179 195/154/177 186/138/172 192/147/180	CLDL-C ≥ 160 TG ≤ 350; if CHD or ≥ 2 risk factor CLDL-C ≥ 130	(54)	63/37 (0/97/3)	12 weeks

* all given once daily in the evening unless specified
bid = twice daily
CLDL-C: calculated LDL-C (Friedewald equation)
LDL-C: directly measured LDL-C

Table 2
US Placebo-Controlled Short-Term Supportive Studies

Study Number	Description	Doses*	Number of Patients: Randomized/ Valid for Efficacy/Co m-pleted	Lipid entry criteria	Age range (mean)	%M/F %B/W/O	Study Duration
D91-012 (0109)	pilot dose-ranging	CER 25µg CER 50µg CER 100µg CER 200µg LOV 40mg PLA	36/35/33 34/34/34 37/36/37 34/32/32 33/32/31 35/35/34	CLDL-C = 160-250 TG ≤ 350	(51)	64/36 (8/91/1)	28 days
D91-016 (0111)	dose-scheduling	CER 100µg bid† CER 200µg qpm‡ CER 200µg qhs° PLA	92/89/90 92/88/91 89/86/87 46/45/44	CLDL-C = 160-250 TG ≤ 350	(52)	59/41 (6/93/1)	28 days
D92-010 (0123)	safety/dose extension	CER 300µg PLA	24/24/23 12/12/12	CLDL-C ≥ 130 TG ≤ 350	(52)	25/75 (6/94/0)	28 days

* all once daily unless specified
† bid = twice daily (with breakfast and dinner)
‡ qpm = once daily with dinner
° qhs = once daily at bedtime
M/F male/female
B/W/O black/white/other

Table 3
Non-US Placebo-Controlled Short-Term Studies

Study Number	Description	Doses*	Number of Patients: Randomized/ Valid for Efficacy/Com-pleted	Lipid entry criteria	Age range (mean)	%M/F %B/W/O	Study Duration
0110 Germany	pilot dose-ranging	CER 25µg CER 50µg CER 100µg CER 200µg SIMVA 20mg PLA	32/30/31 35/31/34 31/28/30 33/30/33 31/29/31 34/30/31	CLDL-C ≥ 160 TG ≤ 350	(50)	61/39 (1/99/0)	28 days
139 ,. Africa	dose-ranging, heterozygous FH	CER 200µg CER 300µg PLA	18/17/18 19/14/18 18/15/18	heterozygous FH: TC >293; LDL-C > 194 with tendon xanthomas	(43)	44/56 (0/74/26)	6 weeks
0149 Canada	safety/dose extension	CER 300µg CER 400µg PLA	140/132/137 138/132/134 71/65/70	CLDL-C ≥ 190 no RF CLDL-C ≥ 160 if ≥ 1 RF; TG ≤ 350	(55)	60/40 (1/98/1)	8 weeks

* all once daily
FH: familial hypercholesterolemia
RF: cardiac risk factors
valid for efficacy: at least 21 days on drug in 0139, 0149; at least 24 days on drug in 0110

Table 4
Non-US Active-Controlled Short-Term Study

Study Number	Description	Doses*	Number of Patients: Randomized/ Valid for Efficacy/Completed	Lipid entry criteria	Age range (mean)	%M/F %B/W/O	Study Duration
0126	2X blind, active-controlled, forced titration q4 wks after 1st 8 wks, goal LDL-C: <130	CER 50µg CER 100µg CER 200µg CER 300µg SIMVA 5mg SIMVA 10mg SIMVA 20mg SIMVA 40mg	260/234/220 ——— 127/117/111	CLDL-C ≥ 160 TG ≤ 350	(52)	61/39 (1/94/5)	32 weeks

* once daily

1 for efficacy: at least 21 days of double blind treatment

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Table 5
US and Non-US Active-Controlled Long-Term Studies

Region/ Study Number	Description	Doses*	Number of Patients: Entered/Valid for Efficacy/Completed	Age range (mean)	%M/F %B/W/O	Study Duration
US X91-031 (X0124)	double-blind, active-controlled long-term extension to Study D91-031	PLA/CER 200µg CER 50µg CER 100µg CER 200µg CER 300µg LOV 40mg ± sequestrant	108/105/89 123/120/97 111/106/90 121/113/102 108/101/97 117/109/99	(56)	54/46 (5/93/2)	18-month extension of 24-week study (2 years total)
Non-US 120	double-blind, active-controlled long-term extension to Study 0120	PLA/CER 25µg CER 25µg CER 50µg CER 100µg CER 200µg SIMVA 20mg ± sequestrant	91/73/83 90/73/78 88/66/77 105/86/95 111/94/101 106/81/96	(55)	56/44 (0/98/2)	21-month extension of 12-week study (100 weeks total)
Non-US X0126	double-blind, active-controlled, titration, long-term extension to Study X0126; goal LDL-C < 130; patients withdrawn if LDL-C ≥ 130 on highest dose of drug	CER 50µg CER 100µg CER 200µg CER 300µg SIMVA 5mg SIMVA 10mg SIMVA 20mg SIMVA 40mg	94/61/33 59/48/35	(54)	63/37 (1/93/60	16-month extension of 8-month study (2 years total)

* all given once daily
sequestrant: bile acid binding resin allowed after entering the long-term extension

Section 6
Human pharmacokinetics

For complete review, see Biopharmaceutics review of the NDA. The material presented here is reproduced from the sponsor's summary and is included here as background to the review of the clinical data contained in the NDA. No study reports or primary data have been reviewed by the medical officer.

Absorption, metabolism, excretion
Cerivastatin is well-absorbed following oral dosing. The absolute bioavailability of a 200 µg oral dose given as either 2 x 100 µg tablets was 60%.
The pharmacokinetics of cerivastatin are linear over the dose range of 50 to The elimination half-life is in the range of 2 to 4 hours; consequently no drug accumulation with once daily dosing is observed. The pharmacokinetics of cerivastatin are similar under fed and fasted conditions.

When ^{14}C-cerivastatin was given as an oral solution, the mean urinary excretion of total radioactivity was 24% of dose, while a mean of 70% was excreted in the feces. Thus, biliary secretion is a major pathway of drug (or metabolite) elimination. Only negligible quantities of ^{14}C were associated with unchanged drug, indicating extensive metabolism. Three metabolites have been identified, and all are present in plasma, urine and feces. Plasma concentrations of all identified metabolites are substantially lower than those of parent drug, and the elimination half-lives are similar. Therefore, while some metabolites have pharmacologic (i.e., HMG-CoA reductase inhibitory) activity, they do not contribute significantly to the overall efficacy of cerivastatin.

Effects of age, renal impairment
Studies to examine the effects of age and gender on cerivastatin pharmacokinetics did not reveal any clinically significant influence of these factors. In a study comparing the pharmacokinetics of cerivastatin in patients with renal impairment and in healthy volunteers, there was no clear relationship between renal function, as measured by creatinine clearance, and cerivastatin pharmacokinetics. Although patients with varying degrees of renal impairment taken as a whole had higher (50 to 100%) AUC and C_{max} values compared to healthy controls, patients with severe renal impairment did not have markedly altered pharmacokinetics.

Drug interactions
A series of drug interaction studies showed that cerivastatin had no effect on the pharmacokinetics of either warfarin or digoxin, and concomitant administration of cimetidine or Maalox® had no effect on cerivastatin. Co-administration of cholestyramine significantly reduced the bioavailability of cerivastatin (by about 20%). However, this effect was greatly diminished when the dosing of the two drugs was separated by 1 or 5 hours.

Cerivastatin is, at least in part, metabolized by the CYP3A4 isozyme. Erythromycin interaction

studies are planned.

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Section 7
Cerivastatin efficacy
Introduction

The efficacy data for cerivastatin are considered against the backdrop of the known efficacy of the class of HMGRIs. More than a decade and a half of research and clinical experience with other members of the class have contributed to a detailed understanding of the mechanism of action of these drugs, which is felt to go beyond simply inhibiting the rate-limiting enzyme in cholesterol biosynthesis and reducing cholesterol output by the liver. More accurately, by inhibiting HMG-CoA reductase and decreasing intracellular cholesterol pools in the liver, an induction of LDL-receptors results, and this increased expression on the surface of the hepatocyte mediates accelerated clearance of LDL with the consequent lowering of steady-state plasma concentrations of LDL particles, and thus of LDL-C.

That HMGRIs work to lower total and LDL-C is well established. In virtually all patients with heterozygous familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia, statins lower total and LDL-C to some degree. In clinical trials, maximum mean effects are seen within 4 to 6 weeks and persist for as long as the drugs are continued. The most predictable treatment failures are patients with homozygous FH and very low LDL-receptor expression, though recently high doses of atorvastatin have been shown to have moderate efficacy in some of these patients. While the reduction in LDL-C at a given dose varies from patient to patient, a dose-response for LDL-C lowering is the rule in all patients.

To date, the principle differences from statin to statin are their potencies in lowering LDL-C. The spectrum of toxicity appears similar across the class and no unique toxic reactions have arisen in patients treated with cerivastatin to date (see safety review). For the most part, the significant adverse reactions to the statins appear related to their primary mode of action. In the liver, for example, for several members of the class, the incidence of transaminase elevations appears correlated with the degree of cholesterol lowering, thus perhaps constituting another marker of the primary pharmacologic effect of the drugs. The effects on muscle, occurring extremely rarely, are presumed due to inhibition of muscle HMG-CoA reductase with resultant cellular injury. The risk of myopathy with at least some members of this class of drugs is known to be increased by co-administration of agents that inhibit CYP3A4, the enzyme responsible for metabolism of these same drugs in the liver. This interaction leads to increased systemic exposure to active statin and the potential for muscle damage.

The preclinical efficacy of cerivastatin, which appeared similar to that of other members of the class, supported its use in clinical trials leading to NDA 20-740. The major thrust of this efficacy review is to establish the absolute potency of cerivastatin in lipid altering. Although, on a per weight basis, cerivastatin is the most potent of the HMGRIs (administered in mcg quantities as opposed to mg quantities of the other statins), the dosage range proposed for marketing effects reductions in LDL and total-C that are at the low end of the spectrum for the marketed HMGRIs. The sponsor makes no comparative efficacy claims in proposed labeling, and thus the task at hand is simply to establish accurately the absolute efficacy of cerivastatin across the dosage range for

purposes of labeling.

7.1 Scope of the efficacy data

The efficacy of cerivastatin in patients with hypercholesterolemia is established by the data from 13 completed randomized clinical trials in the US and abroad (see the tables preceding this section). An additional 15 studies were ongoing at the time of the original NDA submission in June 1996.

Two pilot placebo-controlled dose-ranging studies (0109, 0110), a placebo-controlled safety/dose extension study of cerivastatin 300 mcg (0123), and a dose-scheduling study at 200 mcg daily (0111), all of 4 weeks' duration were followed in the development program by three pivotal placebo- and active-controlled dose ranging studies, one in the US (D91-031, 0124)) and two conducted across multiple centers in Europe, Israel, and South Africa (0132, 0120). In both the US and abroad, extensions of the dose-ranging studies have been completed with exposures out to 2 years. In those trials, placebo patients were switched to active treatment with cerivastatin upon entering the extensions. The long-term extensions were intended largely to increase the overall exposure to cerivastatin, particularly at the higher doses, in order to establish an adequate safety database.

The clinical program also included a double-blind, active-controlled forced-titration-to-goal study conducted in Europe, also extended to 2 years (0126). In addition, a small dose extension safety and efficacy study of 400 mcg dialy was conducted in Canada (0149). The final completed efficacy study was conducted in S. Africa in FH heterozygotes for a treatment duration of 6 weeks (study 0139).

The safety data from the full exposed population have been reviewed in Section 8. The efficacy review will focus on the pivotal studies, and specifically on the intent-to-treat analysis of the lipid data from those three trials. The sponsor has submitted in proposed labeling the results of an analysis of the population "valid for efficacy" which excludes patients who, among other things, received fewer than 21 days of therapy. While the results of the two analyses do not differ substantially, for the purposes of labeling, we prefer the ITT analysis in order to establish the expected lipid changes from baseline to endpoint in response to treatment.

Other analyses presented here will include the time to maximal effect, dose-scheduling, and efficacy by Fredrickson phenotype.

The efficacy in patients with heterozygous FH as well as the results of the dose-extension study comparing cerivastatin 300 and 400 will also be reviewed in brief.

Specific safety results will be reviewed in brief for some of the studies included in the efficacy review. All the other safety data have been reviewed in Section 8.

7.2 Efficacy of cerivastatin in primary hypercholesterolemia and mixed dyslipidemia
Pivotal trials (D91-031, 0120, 0132)
General methods
Study designs (see table listing studies in this NDA, section 5)
Study D91-031 (0124) was a 24-week placebo-controlled, parallel, fixed dose, randomized, double-blind dose ranging study done in the US. This study used lovastatin (LOV) 40mg once-daily as an active comparator.

Study 0120 was a 12-week placebo-controlled, parallel, fixed dose, randomized, double-blind dose ranging study which used simvastatin (SIMVA) 20mg once-daily as an active comparator, and was conducted in Europe, Israel and South Africa.

Study 0132 was a 16-week placebo-controlled, parallel, fixed dose, randomized, double-blind dose ranging study done in Europe, Israel and South Africa which used gemfibrozil (GEM) 600mg twice-daily as an active comparator.

Inclusion criteria
The study populations consisted of ambulatory male and non-childbearing female hyperlipidemic patients (defined above) and the ranges of patient ages in the three studies were as follows: 18 to 75 years (D91-031), 21 to 75 years (0120) and 18 to 80 years (0132).

All patients had primary hyperlipidemias, and the cholesterol and triglyceride cutoffs were chosen to include more individuals with Type II b (mixed dsylipidemia) in the European study (0132). In addition, study 120 adjusted the lipid entry criteria based on cardiac risk factor profiles. Finally, for studies D91-031 and 120, calculated LDL-C (Friedewald formula) was used, and in 0132 (where TG cutoffs were higher) directly measured LDL-C (beta-Quant) was used.

Patients whose calculated LDL-C values were above the lower limit of the criterion entry range after two and four weeks on diet and placebo with both values not differing from the mean value by more than 12% of the mean value, and whose TG values at both of those visits were in the criterion range, and who had a Food Record Rating (FRR) score $\leq$ 15 after four weeks on diet and placebo were eligible for randomization. Patients who failed to randomize because of a high FRR score, failure to meet plasma LDL-C criteria, or scheduling problems were permitted, at the discretion of the investigator, to be re-entered as new patients with a new single-blind number.

Exclusion criteria
Exclusion criteria for the three pivotal studies included: cerebrovascular disease, diabetes mellitus

(defined as a fasting blood sugar > 140 mg/dl); cataracts causing a best-corrected visual acuity of < 20/50; muscular or neuromuscular disease; a serum creatine kinase (CK) elevation ≥ 3 times the upper limit of normal (ULN) in the US and > 3 times the ULN in Europe/Israel/South Africa; liver dysfunction or baseline serum transaminase elevation >1.2 times the ULN in the US and > 2 times the ULN in Europe/Israel/South Africa;significant renal impairment (serum creatinine≥ 2.0 mg/dl); gastrointestinal disorders which could impair absorption; malignancy; or psychosis.

Diet

In all three studies, patients were maintained on the AHA Step I diet or equivalent for a minimum of ten weeks (unless already on the same diet), the last six weeks of which included single-blind placebo. The AHA Step I diet was maintained during the double-blind treatment phase. Dietary counseling was done during the run-in period followed by dietary assessment during the double-blind treatment period in the form of diaries and questionnaires.

Treatment Protocols

In study D91-031, double-blind drug administration consisted of one tablet (CER or PLA) and one capsule (containing a LOV 40mg or PLA tablet) once daily with the evening meal. CER 50, 100, 200, 300μg and PLA tablets were all identical in appearance as were the active and PLA capsules. The double-blind treatment duration was 24 weeks.

In study 120, double-blind drug administration consisted of one tablet (CER or PLA) and one capsule (SIMVA or PLA) administered once daily at bedtime, usually not before 10:00 PM. CER 25μg, 50μg, 100μg, 200μg and PLA tablets were all identical in appearance. The double-blind treatment duration was 12 weeks.

In study 132, double-blind drug administration consisted of one tablet (PLA or GEM 600mg) ½ hour before breakfast, one tablet (PLA or GEM 600mg) ½ hour before the evening meal and one tablet (CER 100μg, 200μg, 300μg or PLA) administered once daily at bedtime. CER 100μg, 200μg, 300μg and PLA tablets were all identical in appearance. The double-blind treatment duration was 16 weeks.

Lipid measurements

Venous blood was obtained after an 11-hour fast. Central, standardized laboratories were used in the US (MRL, Highland Heights, Kentucky) and in Europe (Lille, France).

Efficacy measures

The primary efficacy variable in all studies was percent change from baseline in plasma LDL-C. Secondary variables included changes from baseline in plasma total cholesterol (Total-C), HDL-C, TG and special plasma lipid parameters (Lp (a), Apo AI, Apo B, VLDL-C and directly measured LDL-C using preparative ultracentrifugation [β-Quant]).

Analysis of the efficacy parameters for the pivotal trials were standardized internationally. The US study, D91-031, and one Non-US study, 0120, used calculated LDL-C as the primary

variable, while the Non-US study, 0132, used directly measured LDL-C. The primary timepoint for assessment of efficacy was endpoint, defined as the last valid visit after at least 21 days of treatment post-randomization. The valid for efficacy population was standardized and defined as patients having one valid LDL-C measurement after 21 days. Baseline was defined as the mean of all valid values available at Weeks -4, -2 and 0 (randomization). As mentioned above, the analyses presented here will be of the intent-to-treat (ITT) population, with the last observation carried forward (LOCF).

Results of the pivotal studies

The individual studies will be summarized with regard to study populations, baseline comparability across treatment groups, patient disposition, and compliance. The lipid altering results for all three studies are summarized in a single table following the other information.

D91-031

Baseline characteristics

In study D91-031, the treatment groups were well matched at baseline for gender make-up (50-59% male), race (90-94% white), smoking status, alcohol consumption, family history of dyslipidemia and CHD (50-59% family history of CHD), dietary restriction of cholesterol, recent use of lipid lowering medication, and physical activity.

Patient disposition

Of 939 patients randomized, those taking at least one dose of double-blind medication were valid for safety. The intent-to-treat population had taken double-blind medication and had at least one baseline and on-treatment LDL-C measurement.

Table 7.2.1. Patient disposition: D91-031

	Cerivastatin					
Valid for:	50µg	100µg	200µg	300µg	LOV	PLA
Total	159	157	159	156	154	154
Safety	158	155	159	155	153	154
ITT	**158**	**154**	**159**	**154**	**153**	**152**
Efficacy	145	136	138	137	136	139

A total of 105 patients discontinued: 18, 16, 16, and 21 for the BAY w 6228 50, 100, 200, and 300µg groups respectively, 16 for LOV, and 18 for PLA. The most common reason for discontinuation was an adverse event. Patients discontinuing because of an adverse event numbered four, six, five, and eight for the BAY w 6228 50, 100, 200, and 300µg groups, respectively. There were six patients discontinuing because of an adverse event in each of the LOV and PLA groups.

Adverse events leading to discontinuations included, in the cerivastatin groups, an instance of **arthralgia and myasthenia** that resolved on discontinuation of cerivastatin 200, and an instance of **LFT elevation** in a patient taking cerivastatin 300 that appeared drug-related. One lovastatin-treated patient had diarrhea, dyspepsia, flatulence, and myalgia that resolved on discontinuation of drug, and one placebo patient discontinued due to transaminase elevations of unclear etiology.

Compliance with protocol medication
The compliance with medication was also similar across treatment groups, with fewer than 10% of each group having one or more clinic visits at which less than 70% compliance with study medication (by pill count) was noted.

Study 0132
Characteristics of the randomized population
The sponsor's analyses for patients valid for safety, patients valid for intention to treat and patients valid for efficacy revealed no significant group to group differences at baseline in the major demographic features (age, sex, race) or minor demographic features (alcohol and smoking consumption, duration of hyperlipidaemia, family history of hyperlipidaemia, and family history of coronary artery disease). Across treatment groups, patients were ~98% Caucasian and 50-60% male.

Disposition
A total of 751 patients were randomised (79 in placebo group, 166 in BAY w 6228 100 µg group, 171 in BAY w 6228 200µg group, 175 in BAY w 6228 300µg group and 160 in gemfibrozil group).

A total of 27 patients were excluded from any efficacy analysis, 19 patients due to no measured LDL cholesterol value post-randomisation and 10 patients due to suspected fraud in the center. Thus, a total of 724 patients received double-blind study medication, had a least one baseline plasma LDL-C measurement at visit 3, 4 or 5 prior to randomisation and at least one plasma LDL-C measurement after randomisation, and were thus valid for *intention to treat* analysis. 75 patients received placebo, 160 patients received 100g BAY w 6228, 167 patients received 200g BAY w 6228, 168 patients received 300g BAY w 6228, and 154 patients received 1200mg gemfibrozil.

Table 7.2.2. Patient disposition: Study 0132

		All patients	Placebo	Cer 100	Cer 200	Cer 300	Gem 1200
Randomized patients	N (%)	751 (100)	79 (10.5)	166 (22.1)	171 (22.8)	175 (23.3)	160 (21.3)

Efficacy Analyses						
ITT* - Valid cases	**724**	**75**	**160**	**167**	**168**	**154**
% (valid ITT/N randomised)	96.4%	94.9%	96.4%	97.7%	96.0%	96.3%
ITT*- Invalid cases	27	4	6	4	7	6
Primary efficacy - Valid cases**	**592**	**59**	**131**	**142**	**139**	**121**
% (valid/N randomised)	78.8%	74.7%	78.9%	83.0%	79.4%	75.6%
Primary efficacy** - Invalid cases	159	20	35	29	36	39
Completers* - Valid cases**	**555**	**56**	**123**	**137**	**127**	**112**
% (valid completers/N randomised)	73.9%	70.9%	74.1%	80.1%	72.6%	72.7%
Completers*** - Invalid cases	196	23	43	34	48	48

Dropouts and discontinuations

The table summarizes the reasons for withdrawal from the total randomized study population.

Table 7.2.3. Withdrawals from study 0132

	All patients	Placebo	6228 100 μg	6228 200 μg	6228 300 μg	gemfibrozil 200 mg
N	751	79	166	171	175	160
Any reason*	59*	9	12*	8*	12*	18*
	7.8%	11.4%	7.2%	4.7%	6.9%	11.3%
Adverse events	19	6	2	1	3	7
Death	1	0	1	0	0	0
Patient non-compliance	9	0	3	3	1	2
Consent withdrawn	17	1	4	4	4	4
Insufficient therapeutic effect	1	1	0	0	0	0
Lost to follow-up	5	0	1	1	2	1
Protocol violation	7	0	1	2	2	2
Other	9	1	1	2	2	3

*Note : Patients may have given more than one reason for withdrawal

The one death was sudden in nature and presumed related to existing ischemic heart disease. The adverse events included a 40-year-old female who complained of vivid dreams after 31 days on cerivastatin 300. One patient withdrew because of myalgia after 29 days on therapy (200 mcg) though the CPK was normal. No patient was withdrawn because of persistent CK or LFT

elevations.

Study 0120

Baseline characteristics of the study population

Analyses for patients valid for safety, patients valid for intention to treat, and patients valid for efficacy revealed no significant group to group differences in the major demographic features (age, sex, race) or minor demographic features (alcohol and smoking consumption, duration of hyperlipidaemia, family history of hyperlipidaemia and family history of coronary artery disease), with the exception of family history of coronary artery disease in the valid for efficacy analysis.

The average age was 54-55 years across the treatment groups. There were 51-62% males and the study population was 97-99% white.

Disposition

One thousand, six hundred and three patients were screened for the study, of which 437 were not randomised and were thus invalid for analysis. Eight randomised patients were further invalid for analysis due to no data being recorded on active medication.

One thousand, one hundred and fifty eight patients were valid for the analysis of safety (192 in placebo group, 196 in BAY w 6228 25µg group, 194 in BAY w 6228 50µg group, 195 in BAY w 6228 100µg group, 195 in BAY w 6228 200µg group and 186 in simvastatin group). Twenty-seven patients were excluded from any efficacy analysis due to no lipid measurements on active medication (10 patients) and suspected fraudulent centre (17 patients). Thus 1131 patients were valid for the intention-to-treat analysis of efficacy (187 in placebo group, 193 in BAY w 6228 25µg group, 187 in BAY w 6228 50µg group, 190 in BAY w 6228 100µg group, 191 in BAY w 6228 200µg group and 183 in simvastatin group).

Table 7.2.4. Patient disposition: Study 0120

	Not randomized	Placebo-Cer 25	Cer 25	Cer 50	Cer 100	Cer 200	Simva	Total
No. screened	437	193 (1)	196	195 (1)	197 (2)	197 (2)	188 (2)	1603
Valid for safety		192	196	194	195	195	186	1158

Valid for efficacy-ITT		**187**	**193**	**187**	**190**	**191**	**183**	**1131**
Numbers in parentheses are for patients withdrawn because of no data on double-blind treatment								

Of the randomised patients, 94 prematurely withdrew during the active medication phase of the study (Period B). Reasons for withdrawal were protocol violation (28 patients), withdrawn consent (25 patients), adverse events (21 patients), non-compliance (11 patients), lost to follow-up (5 patients), death (1 patient) and other reasons (15 patients). Other reasons stated were protocol ambiguity (3 patients), LDL-C less than 60 mg/dl, centre closure (2 patients each), wrongly randomised, went for spa treatment, went abroad, post-surgery complications, eating disorder and variable laboratory parameters (1 patient each). Patients may have given more than one reason for withdrawal.

Deaths and discontinuations due to adverse events
Two patients taking cerivastatin died of acute myocardial infarctions during the active treatment period.

The withdrawals due to adverse events are summarized in the table.

Table 7.2.5. Study 0120: Withdrawals due to adverse events

Event	Placebo (n=192)	6228 25µg (n=196)	6228 50µg (n=194)	6228 100µg (n=195)	6228 200µg (n=195)	Simv 20mg (n=186)
Diarrhoea	1(0.5%)	0	0	0	0	0
Meteorism	0	1(0.5%)	0	0	0	0

Nausea/Vomit	1(0.5%)	2(1.0%)	0	0	0	1(0.5%)
Headache	0	0	2(1.0%)	0	0	0
Libido decrease	0	0	0	0	1(0.5%)	0
Insomnia	0	0	1(0.5%)	0	0	0
Ophthalmic	0	0	0	0	0	1(0.5%)
Rash/Pruritus	1(0.5%)	0	0	0	1(0.5%)	0
Pain Back	0	0	0	0	1(0.5%)	0
Oedema Periph	0	0	0	0	0	1(0.5%)
Myasthenia	0	0	0	1(0.5%)	0	0
CPK Increase	0	1(0.5%)	0	1(0.5%)	0	0
ALT/AST Increase	0	0	0	1(0.5%)	0	0

Abdominal symptoms (nausea, vomiting, meteorism, diarrhoea) requiring withdrawal were infrequent, occurring in 0.4% (3/780) of patients treated with BAY w 6228, 1.0% (2/192) patients treated with placebo and 0.5% (1/186) patients treated with simvastatin.

Elevations of CPK resulted in the withdrawal of three patients (44001, 25µg BAY w 6228, peak value 1794 IU/L; 78010, 100µg BAY w 6228, peak value 1552 IU/L; 64016, 25µg BAY w 6228, peak value 1007 IU/L). The investigators assessment of relationship to study medication was 'possible' in the first two cases, and 'remote' in the last case.

Elevations of transaminases resulted in the withdrawal of one patient (71003, 100µg BAY w 6228, peak AST 230 IU/L, peak ALT 377 IU/L). The investigators assessment of relationship to study medication was 'possible'.

Lipid altering results for the pivotal trials

The ITT efficacy data from the pivotal studies will be presented together in order to permit comparison of the results across these similarly designed trials (see table below).

Table 7.2.6. Pivotal studies efficacy results: Intent-to-treat population							
Total Cholesterol							
	Placebo	25	50	100	200	300	Active Control

Study 120							SIMVA
Baseline	296.9	298.7	293.4	294.3	295.4	NA	296.1
% Change	-0.9%	-9.1%	-12.3%	-18.2%	-22.1%		-28.6%
Study 124							LOV
Baseline	281.4	NA	283.9	279.0	281.7	277.8	285.0
% Change	+1.4%		-9.4%	-12.1%	-16.5%	-18.9%	-22.6%
Study 132							GEM
Baseline	307.6	NA	NA	303.7	296.8	305.0	302.2
% Change	+1.6%			-13.1%	-17.8%	-20.3%	-11.9%

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ON ORIGINAL

LDL-C							
	Placebo	25	50	100	200	300	Active Control
Study 120							SIMVA
Baseline	214.6	217.1	212.5	213.0	214.8	NA	214.3
% Change	-0.6%	-11.9%	-15.9%	-24.0%	-29.5%		-38.6%
Study 124							LOV
Baseline	198.0	NA	199.6	196.7	196.6	193.2	200.1
% Change	+1.2%		-13.3%	-18.0%	-24.0%	-27.5%	-31.7%
Study 132							GEM
Baseline	211.2	NA	NA	206.8	201.7	208.6	205.7
% Change	+0.6%			-18.5%	-24.6%	-27.1%	-9.0%

HDL-C							
	Placebo	25	50	100	200	300	Active Control
Study 120							SIMVA
Baseline	52.6	51.8	52.6	51.1	51.9	NA	53.0
% Change	-1.6%	-0.1%	+0.9%	+3.2%	+2.8%		+4.8%
Study 124							LOV
Baseline	50.1	NA	49.7	49.0	50.1	49.4	50.0
% Change	+3.1%		+5.7%	+7.4%	+9.8%	+9.6%	+10.1%
Study 132							GEM
Baseline	43.9	NA	NA	43.3	43.2	44.2	44.4
% Change	+4.8%			+8.2%	+8.7%	+10.3%	+13.9%

Triglycerides							
	Placebo	25	50	100	200	300	Active Control
Study 120							SIMVA
Baseline	148.5	148.6	142.5	153.3	144.9	NA	145.7
% Change	+4.0%	-1.8%	-7.2%	-12.0%	-12.6%		-14.2%
Study 124							LOV
Baseline	167.8	NA	173.3	166.5	175.2	176.6	174.8
% Change	+2.0%		-6.1%	-5.3%	-9.7%	-12.0%	-16.4%
Study 132							GEM
Baseline	289.5	NA	NA	284.6	273.1	275.3	272.5
% Change	-0.1%			-11.3%	-12.3%	-19.5%	-45.9%

As is clear from the table, for LDL-C lowering, the results are fairly consistent across the studies, though the mean response might have been slightly greater in the non-US trial 0120, for unknown reasons. As is the case with other members of the class, there is a dose-response in LDL-C lowering. Again, as with other HMGRIs, there was no dose-response for TG lowering, and likewise no dose-dependent trends in increases in HDL. The effects on TG were generally statistically significantly different from placebo, though the variability across individual patients results in the absence both of a dose-dependent trend and in significant differences from one dose to the next.

When the LDL-C data from the three pivotal trials were pooled (Dr. Mele's analysis), there was a trend toward a greater response among patients 65 and older compared to those under 65 ($p=0.08$), though the differences at each dose were small. There were no effects of gender, baseline weight, Fredrickson phenotype, and baseline LDL-C on the LDL-C lowering response to cerivastatin (data not shown).

Finally, analysis by Dr. Mele of the combined LDL-C data from the three studies reveals a clear dose-response relationship across the 50, 100, and 200 mcg doses. Pairwise comparisons of the dose groups in this pooled analysis showed no statistically significant difference between the 300 mcg and the 200 mcg doses.

Summary of pivotal studies

In patients with primary hypercholesterolemia and mixed dyslipidemia, cerivastatin lowers TC and LDL-C in a dose-related fashion. In addition, though not dose-related, reductions in TG and increases in HDL-C were also observed. The reductions in TG were for the most part, across the studies, statistically significantly different from placebo. The efficacy appears fairly consistent

across the US and non-US studies. No specific safety issues were raised in the individual studies that do not apply to the whole database. Finally, the efficacy data for the US study (D91-031) support the proposed labeling with the caveat that the sponsor's table should be replaced with one summarizing the ITT results. The differences between ITT and valid for efficacy outcomes are very small.

7.3 Supportive results and additional studies

Time to maximal effect/durability of the response

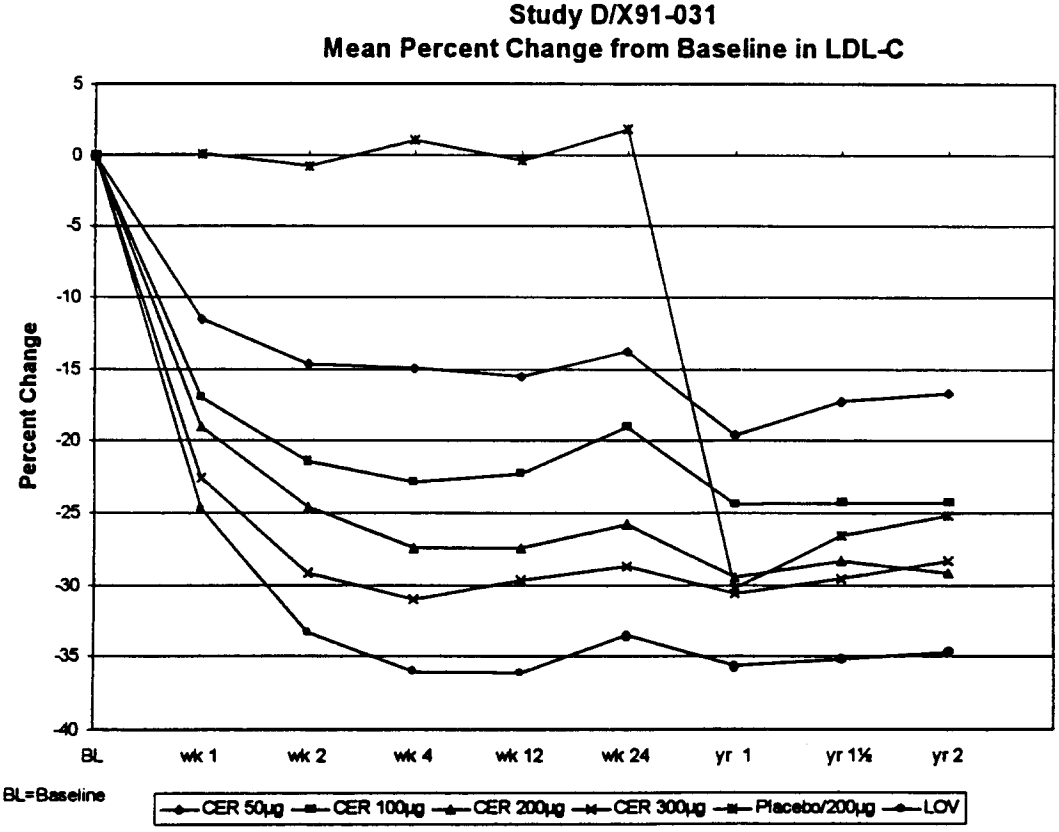
Study D91-031 was extended to 2 years in study X91-031. Patients taking placebo were switched to cerivastatin 200 mcg on entering the extension study. Approximately 100-120 patients in each treatment group chose to enter the long-term extension.

The figure above shows the mean percent change from baseline in LDL-C in the valid-for-efficacy population by time on treatment. As with other statins, the effect on mean LDL-C is apparent by 1 week and maximal by 4 weeks. Thereafter, the effect plateaus and remains stable for the duration of therapy. The fall in the placebo group mean after week 24 is due to the switch to cerivastatin 200 in that group in the extension period.

The results were similar in the other two pivotal trials.

Concomitant use of resins in D/X 91-031

Resin therapy was permitted during the long-term extension. As might have been expected, the use of resins was inversely proportional to the dose of drug, with 47% of patients taking cerivastatin 50 as compared to 17 and 15% of patients taking cerivastatin 300 and lovastatin 40 mg also eventually treated with a sequestrant. In addition, the dose of resin was lowest for the higher doses of cerivastatin and for the lovastatin groups. The use of resins did not markedly change the mean percent reductions from baseline in LDL-C, though the trend toward greater lowering was apparent. When the percentage change from baseline was examined as a function of resin use among the cerivastatin patients, two findings emerged. First, as might have been expected, those destined to take resins had poorer responses to a given dose of cerivastatin than



did those who did not go on to take a resin. Second, addition of the resin brought those patients into line with the no-resin patients with regard to LDL-C lowering.

In summary, as is the case with the other statins, cerivastatin and bile acid binding resins appear to have an additive or synergistic effect on LDL-C lowering.

Dose scheduling (D91-016)

A Phase II dose-scheduling study was performed (Study D91-016) in the US. This study evaluated the effect of CER 200μg administered once daily with the evening meal versus once daily at bedtime. The study also evaluated the efficacy of CER 200μg given as a single dose versus 100μg given twice daily (with breakfast and with the evening meal). The study results for LDL-C are shown in below for the valid-for-efficacy population.

Table 7.3.1. LDL-C lowering: Study D91-016

	CER			
	100μg bid (n=89)	200μg qpm (n=88)	200μg qhs (n=86)	PLA (n=45)
mean baseline (mg/dl)	196.8	196.5	197.3	197.3
mean endpoint (mg/dl)	146.5†	138.9†	137.2†	199.5†
mean change (%)	-25.7%*	-29.4%*‡	-30.4%*‡	+1.4%

bid = twice daily (with breakfast and dinner)
qpm = at dinner
qhs = at bedtime
* significantly different from placebo, $p < 0.05$
† significantly different from baseline, $p < 0.05$
‡ significantly different from CER 100μg bid

The results for total-C lowering followed the same trends. Thus, the data demonstrate that evening dosing (whether at dinner or at bedtime) effects greater average LDL and total-C lowering than the same dose split one-half in the morning and one-half in the evening.
The sponsor has proposed to include the data on LDL-C lowering as a function of timing of dose in the label. This was a relative small study of only 4 weeks' duration. The 29-30% LDL-C lowering for the 200 mcg dose is superior to what was observed across the pivotal trials. To include the apparently more favorable data from the smaller, shorter-term study (that indeed antedated the pivotal trials) is confusing and potentially misleading.

Efficacy in Demographic and Phenotypic Subgroups

Pooled efficacy analyses

The sponsor has pooled the US placebo-controlled studies (D91-031, D91-016, and D91-012) as well as the non-US placebo-controlled studies (0110, 0120, 0132) in order to examine the effect

of cerivastatin across demographic groups and across Fredrickson phenotypes. The analyses are summarized below. The week 4 timepoint was chosen as endpoint for analysis of both data pools, as this was shared by all the studies in each pool. The populations analyzed were valid for efficacy by the criterion of receiving at least 21 days of double-blind therapy. The exceptions were studies D91-012 and D91-016 for which only 7 days of double-blind therapy were required.

In both pools, the treatment groups were well-matched at baseline for sex, race, age, weight, smoking status, alcohol consumption, baseline LDL-C ($\leq$190 versus >190 mg/dL), and Fredrickson phenotype. Type IIa was defined at LDL-C >130, TG<200, and Type IIb was defined as LDL-C >130 and TG >200. Overall, the results showed that the efficacy of cerivastatin was relatively consistent when analyzed by the above variables and for a given dose of drug.

In the US pool, there was a moderate increased effect among females and among older (>65) patients that was seen for the lovastatin treated patients as well. In addition, the use of alcohol appeared to reduce the effect of the drug, though similarly so for lovastatin. The LDL-C lowering effect was consistent between the two Fredrickson phenotypes.

In the non-US pool, the females also appeared somewhat more sensitive overall to cerivastatin, and this was not observed among the simvastatin-treated patients. There was no effect of smoking status, weight, or alcohol consumption. The IIb patients had a slightly greater mean reduction in LDL-C than did the IIa patients.

Efficacy of cerivastatin in FH heterozygotes (study 0139-South Africa)
This was a single center, randomized, placebo-controlled, parallel group study comparing the efficacy of placebo, cerivastatin 200 and cerivastatin 300 in patients with heterozygous FH. Included were male and female patients with FH by genotype, LDL-C >194 mg/dL, with defective of null mutations for LDL-receptor, and between 21 and 75 years of age. After a placebo run-in, patients received placebo, cerivastatin 200, or cerivastatin 300 in double-blind fashion for a mean duration of 49 days (range 34-70). Treatment was extended to one year in some of the patients. The primary efficacy measure was the change in calculated LDL-C from baseline to 6 weeks.

Results
Of 60 patients randomized, 54 (18 in each treatment group) were included in the ITT population. Treatment groups were well matched at baseline for demographic variables, LDL-receptor mutation (null versus defective), and plasma lipids. The table below summarizes the results of the ITT analysis for the principal lipid parameters measured.

Table 7.3.2. Study 0139. Mean percent change in lipids from baseline to 6 weeks

	Placebo (N=18)	Ceriva 200 (n=18)	Ceriva 300 (n=18)
LDL-C			
Baseline	280	281	295
% change	+11%	-17%*	-23%*
TC			
Baseline	348	351	371
% change	+9%	-14%	-19%
HDL-C			
Baseline	46	45	46
% change	+10%	+6%	+9%
TG			
Baseline	110	123	149
% change	+3%	-1%	-20%

The responder analysis with regard to categorical LDL-C reduction for the patients valid for efficacy was presented by the sponsor. All 46 patients valid for efficacy received double-blind study medication until the planned end of the 6-week treatment period, with at least one valid LDL-C value at one of the two last planned visits. This analysis reflects the results of cerivastatin therapy in this small population in those patients presumed most effectively treated.

Table 7.3.3.Study 0139. Categorical response in LDL-C lowering in patients valid for efficacy

Classification	Placebo (n=15)	BAY w 6228 200µg (n=17)	BAY w 6228 300µg (n=14)
≤ 15%	73.33%	29.41%	14.28%
(15%,20%]	13.33%	29.41%	21.42%
(20%,25%]	6.66%	11.76%	21.42%
(25%,30%]	/	17.64%	14.28%
(30%,35%]	/	11.76%	14.28%
(35%,40%]	/	/	14.28%
(50%,60%]	6.66%	/	/

In sum, this study establishes the efficacy of cerivastatin in patients with heterozygous FH. The mean LDL-C lowering at 200 and 300 mcg daily is, as expected, less than that seen in the pivotal studies in patients with (predominantly) non-familial forms of hypercholesterolemia. This is typical of the response in these patients. With this degree of LDL-C lowering on average and in light of the categorical analysis showing that ~60% of patients on 300 mcg had reductions in LDL-C of 30% or less, it is apparent that cerivastatin at these doses will not suffice as monotherapy in this patient population.

Efficacy of cervastatin 400 mcg daily (Study 0149)

This was a double-blind, randomized, multicenter, parallel group, placebo-controlled study to assess the safety and efficacy of cerivastatin 400 mcg daily relative to cerivastatin 300 mcg daily. Though the sponsor has not proposed the 400 mcg dose for marketing thus far, it is anticipated that supplemental applications will be directed at extending the dose of cerivistatin in order to achieve greater efficacy in LDL-C lowering. As such, the principal data from study 0149 are reviewed here.

After a 10-week single-blind placebo, diet, and drug-washout period, patients were randomized to receive placebo, cerivastatin 300, or cerivastatin 400 mcg daily for a double-blind treatment period of 8 weeks. Patients elegible for randomization were ambulatory males and females, aged 18-75, with LDL-C $\geq$ 190, or with LDL-C $\geq$ 160 in the context of one or more cardiac risk factors.

351 patients were randomized, with 2 lost to follow up with no data post randomization. 349 patients were valid for the evaluation of safety: 71 patients treated with placebo, 140 treated with BAY w 6228 300 μg and 138 treated with BAY w 6228 400 μg. Though there were 8 dropouts from this total after randomization, all 349 were included in the ITT analysis. Twenty patients were considered invalid for efficacy analysis by predefined protocol criteria.

Analyses for patients valid for safety, patients valid for intent-to-treat, and patients valid for efficacy revealed no significant treatment group differences for the major demographic and anamnestic variables and no differences for the lipid baseline values. Mean baseline LDL-C was 218-233 mg/dL across the three treatment groups.

The mean duration of therapy was 56 days, with a range of 7 to 49 days, in the ITT population.

Results

The primary efficacy parameter was change from baseline in LDL-C. The table summarizes the mean changes in lipid parameters from baseline to endpoint for the ITT populations.

Table 7.3.4. Study 0149. Efficacy results. Intent-to-treat

	Placebo (n=71)	Ceriva 300 (n=140)	Ceriva 400 (n=138)
LDL-C			
Baseline	232	223	218
% change	+0.2%	-33%	-36%
TC			
Baseline	314	306	300
% change	+1%	-24%	-26%
HDL-C			
Baseline	55	55	54
% change	-0.1%	+6%	+4%
TG			
Baseline	138	142	145
% change	+9%	-17%	-14%

The differences between the cerivastatin 300 μg group and the cerivastatin 400 μg group in mean change from baseline to endpoint in TC and LDL-C were statistically significant. The increased efficacy of the 400 mcg dose is also seen in a responder analysis that shows that the distribution of patients by degree of LDL-C lowering is shifted upward (to greater degrees of LDL-C reduction) in the 400 mcg group.

Table 7.3.5. Responder rates by degree of LDL-C reduction from baseline to endpoint: Valid-for-efficacy analysis

Classification	Placebo (n = 65)	BAY w 6228 300 μg (n = 132)	BAY w 6228 400 μg (n = 132)
≤ 15 %	84.6 %	6.0 %	5.3 %
> 15 % and ≤ 20 %	7.6 %	6.8 %	2.2 %
> 20 % and ≤ 25 %	3.0 %	6.8 %	6.8 %
> 25 % and ≤ 30 %	3.0 %	8.3 %	9.8 %
> 30 % and ≤ 35 %	-	19.6 %	16.6 %
> 35 % and ≤ 40%	-	22.7 %	18.1 %
> 40 % and ≤ 50 %	1.5 %	27.2 %	31.8 %
> 50 % and ≤ 60 %	-	2.2 %	8.3 %
> 60 %	-	-	0.7 %

Safety considerations

Adverse reactions

There were no clinically significant differences in the incidence or spectrum of all or any specific adverse events across the treatment groups. In sum, there were no new symptomatic safety concerns arising at the 400 mcg dose.

Laboratory safety

CK

There were no dose-related increases in the incidence of CK abnormalities, either total or by degree of elevations above normal. Indeed, the rates of all abnormalities were similar between placebo, cerivastatin 300 and cerivastatin 400 dose groups. Few if any of the incidents were clearly related to study drug. No patient discontinued because of a CK abnormality, and there were no elevations to > 10X ULN.

Liver function

Of 349 patients valid for safety analysis, 339 had normal AST at baseline and throughout treatment (96-98% across treatment groups). Five patients who were normal at baseline had increased AST at least once during treatment. All elevations were ≤3 X ULN. The overall incidence of AST elevations on treatment across treatment groups was 1, 2, and 3 cases in the placebo, cerivastatin 300 and 400 groups, respectively.

Of the 349 patients valid for safety, 300 (86-90% across treatment groups) had normal ALT at baseline and throughout the treatment period. Overall, 5, 4, and 7 patients in the placebo, cerivastatin 300, and cerivastatin 400 groups, respectively, had elevations while on drug. None

was > 2X ULN.

In sum, no adverse hepatic effects of cerivastatin were manifest in this small, short term study. Importantly, the 400 mcg dose was not associated with any increase in the rate of LFT abnormalities.

Efficacy of cerivastatin: conclusions

In patients with primary hypercholesterolemia and mixed dyslipidemia, cerivastatin lowers LDL and total-C in a dose-dependent manner, though in the pooled analysis, there was no statistical differences in the responses to 200 and 300 mcg daily. Non-dose-dependent reductions in TG were also seen, as well as non-dose-dependent increases in HDL-C. In head-to-head comparisons, the mean LDL-C reductions in the lovastatin 40 mg and simvastatin 20 mg groups exceeded the responses to cerivastatin 300 and 200 mcg, respectively. The TG-lowering effect of gemfibrozil in study 0132 exceeded that of cerivastatin 300 mcg.

In all, while the dosage range proposed for marketing (50-300 mcg) is limited in absolute potency, the lipid altering effects of cerivastatin are consistent with other members of this class.

Labeling

In concurrence with Dr. Mele's recommendations, the description of the dose-ranging data in the Clinical Studies section of the label should include the ITT analysis of pivotal trial data. The sponsor has chosen the US study. This is acceptable. Furthermore, the timing and duration of response should be supported by a description of the mean effects of treatment on LDL-C. Finally, the dose-scheduling data should be summarized qualitatively in the text and the proposed data table deleted from labeling.