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Scandinavian Simvastatin Study group Nov. 1994, **Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S),** *Lancet* 344 (8934):1383-9

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/s/

William Lubas
7/22/03 04:27:16 PM
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Mary Parks
7/23/03 09:36:48 AM
MEDICAL OFFICER
Concur with recommendations for approval. Please see Team Leader Memo.

5/16/02

MEMO TO DIVISION FILES

NDA# 21-366
Sponsor: IPR Pharmaceuticals Inc.
Drug Name: Crestor™
Category: lipid-lowering agents

Outstanding Issues:

1) Addendum to Financial Disclosure in Medical Officer's Review:

Excluding clinical investigators who "Did not participate" or who "Did not randomize patients" in clinical trials, four out of the fifteen pivotal studies submitted in the original NDA had investigators who did not respond to the request for financial disclosure despite multiple attempts by the sponsor to contact them. These include:

Study 8 Investigator/Center 6

Study 27 Investigator/Center 142, 147, 153, 162, 179

Study 30 Investigator/Center 218

Study 36 Investigator/Center 482

These centers enrolled 9.2%, 8.2%, 0.2% and 0.9% of the patients in each of these studies respectively. Since these investigators enrolled only a small fraction of the patients in each of these trials they were unlikely to bias the final results. But I looked specifically at studies 8 and 27, which had the highest percent of patients involved, to see if the percent lowering of LDL-cholesterol from baseline to 6 and 12 weeks differed if these data points were excluded and I saw no significant difference.

In conclusion, there is no reason to suspect study bias from the financial disclosure data.

William Lubas MD-PhD

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/s/

William Lubas
5/14/02 05:42:41 PM
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Mary Parks
5/16/02 10:15:40 AM
MEDICAL OFFICER

5/2/02

MEDICAL OFFICER REVIEW

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

Application #: 21-366 | **Application Type:** NDA
Sponsor: IPR Pharmaceuticals Inc. | **Proprietary Name:** Crestor™
Investigator: Multiple (Not named) | **USAN Name:** Rosuvastatin calcium
Category: Lipid-lowering agent | **Route of Administration:** Oral
Reviewer: William Lubas MD-Phd | **Review Date:** 4/29/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
	June 26, 2001	Original application	Clinstat, labeling, other
	Aug. 9, 2001		Pharm Tox update
	Aug. 17, 2001		Patent information
	Aug. 23, 2001		Clinstat NCEP III update, labeling
	Oct. 22, 2001		4 month SUR Clinstat, PharmTox
	Oct. 30, 2001		Clinstat updates
	Nov. 2, 2001		CMC update
	Dec. 6, 2001		Patent information update
	Jan. 23, 2002		CMC update
	Feb. 7, 2002		PreApproval Safety Update
	Feb. 13, 2002		Patient Narrative update
	Feb. 18, 2002		CRF update
	Feb. 21, 2002		Gemfibrozil study, PK data

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

See Executive Summary

OUTSTANDING ISSUES:

See Recommendations on Phase 4 Studies and/or Risk Management Steps

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____		Clinical Hold	_____ Study May Proceed
NDA, Efficacy/Label supplement: ___X___		Approvable	_____ Not Approvable

SIGNATURES: **Medical Reviewer:** William Lubas MD-PhD **Date:** 4/29/02

Medical Team Leader: Mary Parks MD. **Date:** 4/29/02

Table of Contents

Clinical Review for NDA 21-366

Executive Summary

1. Recommendations

1.1. Recommendation on Approvability

It is recommended that daily doses of —— 5 mg of rosuvastatin be approved for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB), once any outstanding chemistry issues with respect to these doses are resolved.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

Approvability of the daily doses of 10 and 20 mg would depend on the long-term safety profile of daily doses of 20 and 40 mg in the ongoing clinical trials. Adequate exposures of at least 600 patients at 6 months and 200 patients at one year would be required with the 20 mg daily dose to permit marketing of 10 mg. Similarly, adequate exposure with the 40 mg daily dose in clinical trials would be required to permit marketing of 20 mg.

Approvability of the 40 mg daily dose would also depend on further clinical trials to show that the renal safety findings of proteinuria and hematuria, are reversible and not associated with a progression in serum creatinine levels.

Approval of the 80 mg daily dose is not recommended as the risks of renal disease, myopathy and rhabdomyolysis do not out weigh the benefits of a marginal decrease of 3-5% in LDL-cholesterol compared to 40 mg.

The maximum recommended daily dose for rosuvastatin in patients on cylcosporine or with severe renal or severe hepatic disease is —. Approvability of higher doses will depend on the safety profile of the 20 and 40 mg doses in ongoing clinical trials, and on the results of long-term safety trials in these patient populations.

The maximum recommended daily dose of rosuvastatin in combination with gemfibrozil is — mg. Approvability of higher doses will depend on the safety profile of the 20 and 40 mg doses in ongoing clinical trials.

2. Summary of Clinical Findings

2.1. Brief Overview of Clinical Program

Rosuvastatin is the newest member of the statin class of lipid-lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. The sponsor proposes to market rosuvastatin as a once daily oral formulation with a starting dose of 10 mg and a dosing range of 10, 20, 40 and 80 mg. The clinical program was designed to show that rosuvastatin is effective at

- lowering total and LDL-cholesterol in patients with familial and nonfamilial hypercholesterolemia (Fredrickson Type IIA and IIB)
- lowering triglycerides in patients with Fredrickson Type IIB and IV dyslipidemia and
- lowering cholesterol levels in patients with homozygous familial hypercholesterolemia as an adjunct to other treatment modalities (e.g., LDL-apheresis) or if such treatments were unavailable.

2.2. Efficacy

Rosuvastatin was effective at producing a significant reduction in the % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol and ApoB in subjects with Fredrickson type IIA and IIB dyslipidemia at daily doses from 1 to 80 mg compared to placebo. The % changes from baseline in LDL-cholesterol ranged from 1 mg (-33%) to 80 mg (-65%). Most patients reached NCEP target LDL-cholesterol on 5 or 10 mg of rosuvastatin (67 and 81%, respectively). Increasing the daily dose from 20 to 80 mg resulted in only an additional 3 to 4 % of patients reaching NCEP goals. While increases in mean % change from baseline of HDL-cholesterol and decreases in mean % change from baseline of triglycerides were seen for daily doses from 1 mg to 80 mg there was no dose-response relationship and the values were not statistically significant at all doses. However, patients with low HDL-cholesterol at trial entry, <34 mg/dl, had greater increases in HDL-cholesterol on 5 to 10 mg of rosuvastatin than patients with HDL ≥ 35mg/dl (15.6% vs. 7.3%). Similarly, patients with Type IIB dyslipidemia (TG> 200mg/dl at baseline) had greater mean decreases from baseline in TG than patients with Type IIA (TG<200 mg/dl at baseline, -23.1% vs. -11.8%). An insufficient number of African Americans, Hispanics and Asians were included in these studies to independently confirm the efficacy in these subpopulations.

Executive Summary Section

Rosuvastatin was effective at producing statistically significant reductions in the mean % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol, ApoB and HDL-cholesterol in subjects with severe hypercholesterolemia (LDL-cholesterol > 220mg/dL) at daily doses of 20, 40 and 80 mg compared to similar doses of atorvastatin. Both treatments produced a decrease in triglycerides over this same dose range that was not statistically significant between treatments.

Rosuvastatin in combination with cholestyramine (16g) in subjects with severe hypercholesterolemia (LDL-cholesterol > 190mg/dL) appeared to be more effective at lowering LDL-cholesterol than rosuvastatin (80 mg) monotherapy, but the difference was not statistically significant.

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol, and ApoB in subjects with homozygous familial hypercholesterolemia (mean baseline LDL-cholesterol of 515 ± 115 mg/dl) at daily doses of 20, 40 to 80 mg, but there was little additional benefit for daily doses greater than 20 mg. All three doses provided similar mean reductions in LDL-cholesterol from baseline (-20%, -24%, and –22%, respectively). Joy Mele's statistical review shows that approximately one-third of patients titrated to doses higher than 20 mg did achieve an additional 6% lowering in LDL-cholesterol, which corresponds to an additional decrease of about 30 mg/dl. It is this medical reviewer's opinion that these additional small decreases in LDL-cholesterol are unlikely to have much clinical impact in these patients whose mean LDL-cholesterol are still > 400 mg/dl. Changes in HDL-cholesterol and triglycerides were variable.

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline triglycerides in subjects with Fredrickson type IIB and IV dyslipidemia at daily doses from 5 to 80 mg compared to placebo. The mean dose response curve was flat at doses above 10 mg whereas the median dose-response curve was suggestive of a dose response relationship. These data suggest that a subset of patients were poor responders to higher doses.

Rosuvastatin in combination with niacin in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin. Rosuvastatin in combination with niacin appeared to be more effective at decreasing triglycerides than monotherapy with either drug alone but it was not statistically significant.

Rosuvastatin in combination with fenofibrate in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at decreasing triglycerides than monotherapy with rosuvastatin. Rosuvastatin in combination with fenofibrate appeared to be more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin alone but it was not statistically significant.

Rosuvastatin was effective at lowering LDL-cholesterol in both men and women and in older and younger populations. The 10 mg daily dose appeared to be slightly more effective in women and in older patients (>65 y/o) than the 5 mg dose. Postmenopausal women showed the greatest response to the 10 mg dose. The difference was not robust enough to affect proposed dosing.

Rosuvastatin appears to be effective in Caucasians, Blacks, Hispanics, and Asians. However, the number of patients in the non-Caucasian subgroups is too small to draw any meaningful comparisons. A PK study in healthy Japanese volunteers showed an approximately two-fold increase in AUC and Cmax for rosuvastatin in Japanese patients compared to their Western counterparts (see Special Populations below).

Rosuvastatin showed a trend towards more LDL-cholesterol reduction in patients with worsening renal function (see Special Populations below). In contrast, rosuvastatin showed a trend towards less LDL-cholesterol reduction in patients with worsening liver function.

2.3. Safety

There is an increase in the frequency of hepatic, musculoskeletal and renal adverse events in patients on rosuvastatin compared to those on placebo.

Rosuvastatin, like other statins, shows a dose-related increase in liver transaminases. The frequency of multiple transaminase elevations on 80 mg of rosuvastatin is 1.1% similar to what has been seen with the highest approved dose of other statins (1.5-2.7%). No cases of liver failure or unexplained hepatitis were observed in these trials. Liver function monitoring permitted identification of subjects with persistent elevations who required adjustments in their drug dosage.

A higher frequency of myopathy (1.1%) and rhabdomyolysis (0.5%) was observed in clinical trials with rosuvastatin than had previously been reported for any of the currently approved statins. Most cases of myopathy (14/19=74%) and all six cases of rhabdomyolysis occurred at the highest

dose, 80 mg. A few cases of myopathy were seen at doses of 5 to 20 mg but they were confounded by a history of vigorous exercise or physical injury. The number of patients exposed and the duration of exposure at doses of 5 and 10 mg were similar to that at 80 mg but no cases of rhabdomyolysis were seen at these lower doses. However, the exposure at doses of 20 and 40 mg was less than 1/3 the subject-years of exposure at 80 mg, so the safety of these doses cannot be adequately assessed. After drug approval the number of patients exposed to drug will greatly exceed that seen in these clinical trials and so even a low incidence of rhabdomyolysis observed in this NDA may translate into a substantial number of cases post-marketing. Experience with previously approved statins has revealed a 0% incidence of rhabdomyolysis in the NDAs reviewed premarketing. Post-approval, with marketing of the statins to a larger, more diverse patient population without the close surveillance associated with clinical trial conduct, rhabdomyolysis has been reported with all the statins. A recent review of the AERS database covering the 29 month time frame between Nov. 1997 and March 2000 found the following number of cases of statin-associated rhabdomyolysis: simvastatin 215, > cerivastatin 192, > atorvastatin 73, > pravastatin 71, >lovastatin 40, > fluvastatin 10 (Omar and Wilson, Feb. 2002). Therefore, since it is known that this drug is already associated with a serious and potentially life-threatening adverse event despite the controlled environment of a clinical trial, it is prudent to limit initial exposure to this drug to multiples of the no adverse event level to provide a safety margin. Since the highest dose with an adequate safety exposure was 10 mg, I would only recommend initial approval of doses up to 5 mg. As the sponsor collects adequate long-term safety data at doses of 20 and 40 mg, approvability of doses of 10 and 20 mg could be reconsidered.

Unlike CK and transaminase elevations, which have previously been reported for other statins, rosuvastatin is the first statin to be associated with the development and progression of proteinuria and hematuria. The effect was most pronounced at the 80 mg dose but was also evident at 40 mg. Proteinuria, with or without hematuria, was associated with a mean % increase in serum creatinine in these patients. In about 30% of the patients it persisted at the same level or progressed. Proteinuria was associated with an increase in beta-2-microglobulin and N-acetyl-beta-D-glucosaminidase suggestive of renal tubular damage. Two cases of renal failure and one of renal insufficiency of unknown etiology were observed on the 80 mg dose. These cases were also associated with mild proteinuria, hematuria and evidence of tubular inflammation or necrosis. It is not known at this time if the proteinuria, hematuria and increase in serum creatinine are reversible after the drug is discontinued. Routine urinalysis testing for patients taking 40 mg or more of rosuvastatin in

clinical trials is recommended. For patients with persistent or progressive proteinuria, or with evidence of an increase in serum creatinine, it is recommended that the dose be lowered or the drug discontinued. Approvability of 40 mg and higher doses would depend on further clinical trials to show that the renal effects are reversible and not associated with a progressive increase in serum creatinine levels.

2.4. Dosing, Regimen and Administration

Rosuvastatin was studied at single daily oral doses of 1, 2.5, 5, 10, 20, 40 and 80 mg. The sponsor proposed a starting dose of 10 mg daily with a dose range of 10 to 80 mg once daily for patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB). The sponsor proposed the option of a daily start dose of 20 mg for patients with heterozygous or homozygous familial hypercholesterolemia, with severe hypercholesterolemia (LDL-cholesterol >190mg/dl), with a dose range up to 80 mg.

Because of the risks of renal disease, myopathy and rhabdomyolysis associated with the higher doses of rosuvastatin (see Safety 2.3.) this medical reviewer would recommend the approval of only the 1, 2.5 and 5 mg doses at this time. Since the sponsor had not originally planned to market these low doses, any outstanding chemistry issues with respect to these doses would need to be resolved before they could be approved.

2.5. Drug-Drug Interactions

Heart transplant patients treated with cyclosporine and receiving daily doses of 10 mg of rosuvastatin had a 10.6 to 12.6 fold increase in Cmax and a 7.1 to 7.8 fold increase in AUC (0-24) for rosuvastatin compared to values obtained in healthy subjects.

Healthy subjects receiving 600 mg twice daily of gemfibrozil had a 2.2 fold increase in Cmax and a 1.9 fold increase in AUC (0-t) for rosuvastatin after a single 80 mg dose compared to placebo.

Healthy subjects receiving 20 ml of co-magaldrox, a magnesium hydroxide antacid, simultaneously with 40 mg of rosuvastatin had a 50% decrease in Cmax and a 54% decrease in AUC (0-t) for rosuvastatin compared to subjects receiving rosuvastatin alone. When co-magaldrox was taken 2 hours after rosuvastatin the reduction was smaller with a 16% decrease in Cmax and a 22% decrease in AUC (0-t).

Healthy subjects receiving 40 mg of rosuvastatin daily for 10 days and a single 25 mg dose of warfarin on day 7 had no clinically relevant changes

in AUC (0-t) or Cmax for rosuvastatin. However, there was a prolongation of prothrombin times in all subjects, median time to max INR was 36 hours after warfarin dosing in the placebo period compared to 42 hours after warfarin dosing in the rosuvastatin period. Patients who are to receive warfarin and rosuvastatin concomitantly will need to have INR measurements with changes in rosuvastatin dosing in addition to routine monitoring for warfarin.

In-vitro data suggest that rosuvastatin is not metabolized by CYP3A4 to a clinically significant extent. No clinically relevant changes in AUC (0-t) or Cmax for rosuvastatin were seen when it was administered with known CYP3A4 inhibitors such as itraconazole, ketoconazole and erythromycin.

No clinically relevant changes in AUC (0-t) or Cmax were seen for rosuvastatin when it was administered with the known CYP2C9 inhibitor fluconazole.

2.6. Special Populations

Subjects with severe renal impairment, (baseline CrCL < 30ml/min), had a 3.1-fold increase in Cmax and a 3.2 fold increase in AUC (0-24) for rosuvastatin compared to healthy subjects treated with 20 mg of rosuvastatin.

Subjects with alcohol-induced cirrhosis of the liver described as severe by the Maddrey discriminant function (df≥54) had a 4 to 16 fold increase in Cmax and a 2 to 4 fold increase in AUC (0-24) for rosuvastatin compared to patients with normal hepatic function treated with 10 mg of rosuvastatin.

After single or seven-day repeat oral dosing with 20 mg of rosuvastatin, Cmax was 1.9 to 2.3 fold higher and AUC (0-24) was 2.0 to 2.5 fold higher for rosuvastatin in healthy Japanese male volunteers compared to their Western counterparts.

No specific safety concerns were identified in these special population trials with respect to rosuvastatin. However, since the number of subjects enrolled in these trials was low (Renal-impaired study N=26, Hepatically impaired study N=18, Japanese study N=18), and most studies lasted at most 2 weeks, the safety profile of rosuvastatin in these special populations can not be adequately assessed based on the results of these trials alone. It is recommended that the PK data from these trials be used to determine the maximum permitted dose in each population until better long-term safety data in these populations become available.

Clinical Review

1. Introduction and Background

1.1. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Rosuvastatin (Crestor™) is a member of the statin class of lipid lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. There are five currently marketed statins: atorvastatin, pravastatin, simvastatin, fluvastatin, and lovastatin. Statins are currently approved for the treatment of adults with the following lipid disorders:

a) to reduce elevated LDL-cholesterol, total cholesterol, Apo B and TG levels and to increase HDL levels in patients with primary hypercholesterolemia and Fredrickson Type IIA and IIB

b) to reduce elevated levels of TG in patients with Fredrickson Type IV

c) to reduce LDL-cholesterol and total cholesterol in patients with homozygous familial hypercholesterolemia

d) to treat patients with primary dysbetalipoproteinemia, Fredrickson Type III

The sponsor has submitted data in this NDA to support the use of single daily oral doses of 10, 20, 40 and 80 mg of rosuvastatin for indications a, b and c above in men and women > 18 years of age.

2. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Sharon Kelly, Ph.D, reviewed the chemistry data.

John Gong, Ph.D, reviewed the animal pharmacology and toxicology data.

Cynthia Liu, M.A. and Joy Mele, M.S performed the statistical reviews of the efficacy data.

3. Human Pharmacokinetics and Pharmacodynamics

Sang M. Chung, Ph.D. and He Sun, Ph.D reviewed the PK/PD data. A brief summary of pertinent clinically relevant PK/PD information is provided.

Heart transplant patients treated with cyclosporine and receiving daily doses of 10mg of rosuvastatin had a 10.6 to 12.6 fold increase in Cmax and a 7.1 to 7.8 fold increase in AUC (0-24) compared to values obtained during multiple dosing studies in healthy subjects.

Healthy subjects receiving 600 mg twice daily of gemfibrozil had a 2.2 fold increase in Cmax and a 1.9 fold increase in AUC (0-t) after a single dose of 80 mg of rosuvastatin compared to placebo.

Healthy subjects receiving 20 ml of co-magaldrox, a magnesium hydroxide antacid, simultaneously with 40 mg of rosuvastatin had a 50% decrease in Cmax and a 54% decrease in AUC (0-t) compared to subjects receiving rosuvastatin alone. When co-magaldrox was taken 2 hours after rosuvastatin the reduction was smaller with a 16% decrease in Cmax and a 22% decrease in AUC (0-t).

Healthy subjects receiving 40 mg of rosuvastatin daily for 10 days and a single 25 mg dose of warfarin on day 7 had no clinically relevant changes in AUC (0-t) or Cmax for rosuvastatin. However, there was a prolongation of prothrombin times in all subjects, median time to max INR was 36 hours after warfarin dosing in the placebo period compared to 42 hours after warfarin dosing in the rosuvastatin period. Patients who are to receive warfarin and rosuvastatin concomitantly will need to have INR measurements with changes in rosuvastatin dosing in addition to routine monitoring for warfarin.

In-vitro data suggest that rosuvastatin is not metabolized by CYP3A4 to a clinically significant extent. No clinically relevant changes in AUC (0-t) or Cmax were seen when rosuvastatin was administered with known CYP3A4 inhibitors such as itraconazole, ketoconazole and erythromycin.

No clinically relevant changes in AUC (0-t) or Cmax were seen for rosuvastatin when it was administered with the known CYP2C9 inhibitor fluconazole.

4. Description of Clinical Data and Sources

4.1. Overall Data

The sponsor submitted all data electronically. Data consisted entirely of clinical trials performed as part of the sponsor's clinical trial program.

4.2. Tables Listing the Clinical Trials

Table 1 Controlled Clinical Trials		
Trial number	Trial Design	Subjects
1	Dose ranging 5-40 mg	Healthy male volunteers
2	Single/repeat dose	Healthy male volunteers
7	Single/repeat dose	Healthy Japanese male volunteers
8	Dose response 1- 40 mg	Type IIa/IIb
9	Effect on oral contraceptives	Healthy volunteer females
11	Single/repeat dose	Healthy male volunteers
12	Effect of itraconazole on PK	Healthy male volunteers
13	Effect of digoxin on PK	Healthy male volunteers
14	Effect of warfarin on PK	Healthy volunteers
23	Dose response 40-80 mg	Healthy volunteers
24	Efficacy and Safety 5-10 mg	Type IIa/IIb
25	Efficacy and Safety 5-80 mg	Type IIa/IIb with CHD or type 2 DM
26	Efficacy and Safety 5- 80mg	Type IIa/IIb
27	Efficacy and Safety 5-10 mg	Type IIa/IIb
28	Efficacy and Safety 5-80 mg	Type IIa/IIb
29	Efficacy and Safety 5-80 mg Combination with niacin	Type IIb/IV
30	Efficacy and Safety 20-80 mg	Heterozygous familial HC
31	Efficacy and Safety 40-80 mg Combination with cholestyramine	Severe HC
33	Efficacy and Safety 5-80 mg	Type IIa/IIb
35	Efficacy and Safety 5-80 mg	Type IIb/IV
36	Efficacy and Safety 5-80 mg Combination with fenofibrate	Type IIb/IV
48	Effect of fluconazole on PK	Healthy male volunteers
53	Effect of itraconazole on PK	Healthy male volunteers
54	Efficacy and Safety 20-80 mg	Homozygous familial HC
56	Effect of ventricular repolarization	Healthy volunteers
57	Effect of ketoconazole on PK	Healthy male volunteers
58	Effect of erythromycin on PK	Healthy male volunteers
64	Effect on ECG parameters	Healthy male volunteers
95	Effect of gemfibrozil	Healthy volunteers
1812	Dose Response 10-20 mg	Healthy Japanese male volunteers
1814	Repeat dose 10 mg	Healthy Japanese male volunteers
1815	Dose Response 0.5-2 mg	Healthy Japanese male volunteers

Table 2 Uncontrolled Clinical Trials		
Trial number	Trial Design	Subjects
3	Metabolism & Excretion	Healthy male volunteers
4	Effect of time on dose	Healthy volunteers
5	Effect of food on dose	Healthy volunteers
6	Bioequivalence caps vs. tabs	Healthy male volunteers
10	Absolute bioavailability	Healthy male volunteers
15	Effect of gender and age on dose	Healthy volunteers
17	Effect of renal impairment	Renal impaired volunteers
18	Effect of liver impairment	Liver impaired volunteers
19	Bioequivalence caps vs. tabs	Healthy volunteers
20	Effect of co-magaldrox	Healthy male volunteers
21	Effect of cyclosporine	Cardiac transplant volunteers
22	Effect of fenofibrate	Healthy male volunteers
34	Long term Safety and Efficacy	Type IIa/IIb or IV
47	Dose proportionality	Healthy male volunteers
49	Bioequivalence caps vs. tabs	Healthy volunteers
60	Effect of warfarin	Healthy volunteers
63	Absolute bioavailability	Healthy Japanese male volunteers
1811	Dose ranging 0.5- 20 mg	Healthy Japanese male volunteers
1821	Efficacy and Safety 1-4 mg	Type IIa/IIb Japanese subjects

4.3. Postmarketing Experience

None

5. Clinical Review Methods

5.1. How the Review was Conducted

Individual trials were reviewed for efficacy, PK data and drug-drug interactions. Pooled data from the phase 2 and 3 trials were used for the safety analysis.

5.2. Overview of Materials Consulted in Review

CDER Stamp Date	
June 26, 2001	Original clinical submission including SAS data files, case report forms and proposed labeling
Aug. 9, 2001	Pharm Tox update- 13 week Rat oncogenicity study
Aug. 17, 2001	Patent information
Aug. 23, 2001	Clinstat- NCEP III update and proposed changes to labeling
Oct. 22, 2001	Clinstat -4 month SUR including new SAS data files, PharmTox 13 week rat study
Oct. 30, 2001	Clinstat- errata updates
Nov. 2, 2001	CMC- drug stability and dissolution update
Dec. 6, 2001	Patent information
Jan. 23, 2002	CMC- batch analysis

Feb. 7, 2002	Pre Approval Safety Update including SAS data files
Feb. 13, 2002	Patient Narrative update
Feb. 18, 2002	CRF update
Feb. 21, 2002	Gemfibrozil study, PK data

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audited three domestic sites to confirm data quality and integrity.

Dr. Jeffery T. Whitmer
Cincinnati, Ohio
protocols #4522IL/0033, 0034, and 0035

Dr. Leonard Keilson
Portland, Maine
protocols #4522IL/0031, and 0034

Dr. B. Zedler
Richmond, Virginia
protocols #4522IL/0024, 0028, and 0034

These sites were noted to have adhered to pertinent federal regulations and/or good clinical investigational practices governing conduct of clinical investigations and protection of human subjects.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes

5.5. Evaluation of Financial Disclosure

The sponsor submitted Financial Disclosure Data from Clinical Investigators involved in 29 clinical trials. Data for the pivotal trials 8, 23, 24, 25, 26, 27, 28, 29, 33, 35, 36 were included. Only one investigator, [redacted] was involved in three trials 8, 26 and 30 where he enrolled 6%, 2% and 1% of the randomized patients. Since this investigator enrolled only a small fraction of the patients in each of these double blind controlled trials it is unlikely that he could have substantially biased the final results.

6. Integrated Review of Efficacy

6.1. Brief Statement of Conclusions

1) Rosuvastatin was effective at producing significant reduction in the % change from baseline in LDL-cholesterol, total cholesterol, non HDL-cholesterol and ApoB in subjects with Fredrickson Type IIA and IIB and primary hypercholesterolemia.

2) Rosuvastatin was effective at producing significant reduction in the % change from baseline in TG in patients with Fredrickson Type IIB and IV.

3) Rosuvastatin was effective at producing significant reduction in the % change from baseline in LDL-cholesterol, total cholesterol, non HDL-cholesterol and ApoB in subjects with homozygous familial hypercholesterolemia.

6.2. General Approach to Review of the Efficacy of the Drug

The efficacy of rosuvastatin in lowering LDL-cholesterol was studied

- in patients with mixed dyslipidemia (Fredrickson IIA and IIB), trials 8, 23, 24, 25, 26, 27, 28, and 33,
- in patients with heterozygous familial or nonfamilial hypercholesterolemia, trials 30 and 31 (±Cholestyramine), and
- in patients with homozygous familial hypercholesterolemia trial 54.

The efficacy of rosuvastatin in lowering triglycerides in patients with Fredrickson IIB and IV was studied in trials 29 (±Niacin), 35, and 36 (±Fenofibrate).

6.3. Detailed Review of Trials by Indication

6.3.1 MIXED DYSLIPIDEMIA (FREDRICKSON IIA AND IIB)

Rosuvastatin was studied in patients with mixed dyslipidemia in randomized, double blind, trials 8, 23, 24, 25, 26, 27, 28, and 33.

Table 3 Trials Supporting the Basic and Comparative Efficacy of Rosuvastatin in Subjects with Type IIA/IIB Dyslipidemia

Trial No.	Design/principal location	N[a]	Mean age Gender	Rosuvastatin dose (mg/day)	Comparator dose (mg/day)	Baseline LDL-C (mg/dL)	Time[b] of primary endpoint ΔLDL-C (%)
8	Randomized, DB, placebo controlled, dose-ranging; Europe	142	55 y 94 m 48 f	1/2.5/5/10/20/40	Placebo Atorvastatin 10/80 (open-label)	160-<220	6 w
23	Randomized, DB, placebo controlled, dose-ranging; Europe	64	58 y 35 m 29 f	40/80	Placebo	160-<220	6 w
24	Randomized, DB, placebo controlled, active controlled; USA/Canada	519	57 y 240 m 279 f	5/10	Placebo Atorvastatin 10	160-<250	12 w
25	Randomized, DB, active controlled, force-titration; USA/Canada	383	62 y 232 m 151 f	5/10/20/40/80	Atorvastatin 10/40/80	160-<250	24 w
26	Randomized, DB, active controlled, titration to NCEP II goals up to 52 weeks; Europe	412	57 y 233 m 179 f	5/10/20/40/80	Atorvastatin 10/20/40/80	160-<250	12 w
27	Randomized, DB, active controlled; Europe	502	59 y 238 m 264 f	5/10	Pravastatin 20 Simvastatin 20	160-<250	12 w
28	Randomized, DB, active controlled, titration to NCEP II goals up to 52 weeks; USA/Canada	477	59 y 186 m 291 f	5/10/20/40/80	Pravastatin 20/40 Simvastatin 20/40/80	160-<250	12 w
33	Randomized, DB, active controlled, dose-ranging; USA/Canada	374	57 y 194 m 180 f	5/10/20/40/80	Atorvastatin 10/20/40/80	160-<250	6 w

Table 3 ISE, Data derived from Table T1 in the individual trial reports.

[a] N refers to total number of subjects randomized to treatment.

[b] In this set of trials, the primary endpoint measurement was at the time of trial completion, except for Trials 26 and 28 which continued for a total duration of 52 weeks.

DB = double blind; f = female; m = male; y = years; w = weeks.

Trials 8 and 23 were conducted utilizing a similar 16-week, multi-center, randomized, double blind, and parallel-group trial design. After a 6 week dietary run in period, subjects were randomized to daily doses of 1, 2.5, 5, 10, 20, 40 or 80 mg of rosuvastatin or placebo. This was followed by a 4-week follow up period to ensure subjects returned to pre-trial baseline levels. Trials included males 18 to 70 years of age and post-menopausal females 50 to 70 years of age. Subjects had fasting LDL-cholesterol concentrations > 160 mg/dl and < 240 mg/dl, and fasting triglyceride levels of < 300mg/dl. Trial medication was given once daily 3 hours after the evening meal. Trial 8 randomized 142 subjects into treatment groups containing between 13 and 18 patients receiving 1 to 40 mg of rosuvastatin or placebo. Trial 23 randomized 64 subjects into treatment groups receiving placebo (N=17), 40 mg (N=16) and 80 mg (N=31) of rosuvastatin. The primary endpoint was percentage change from baseline to week 6 in LDL-cholesterol. The secondary endpoints were percent change from baseline to week 6 for HDL-cholesterol, TG, total cholesterol, ApoA-I, ApoA-II, Lp(a), ApoB, and fibrinogen. The mean baseline LDL-cholesterol values ranged from 184 to 197 mg/dl for all treatment groups in both studies. The mean change from baseline of the placebo group was slightly greater in study 8 compared to study 23 (-7.3 vs. –0.4 mg/dl). The results of the pooled data from both studies are shown in Table 4.

Table 4

Rosuvastatin Dose Response vs. Placebo in % Change from Baseline to Week 6 in Lipids in Type IIA/IIB Dyslipidemia: Trials 8 and 23 Pooled[a]

Efficacy endpoint	Placebo	Rosuvastatin dose						
		1.0 mg	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg
	(N=31)	(N=14)	(N=15)	(N=18)	(N=17)	(N=17)	(N=34)	(N=31)
LDL-C								
BL, mg/dL	194	191	190	191	190	191	185	188
Ls mean %	-3.8	-33.2***	-39.6***	-42.6***	-49.8***	-53.1***	-62.2***	-64.9***
change (SE)	(1.7)	(2.8)	(2.7)	(2.6)	(2.6)	(2.6)	(1.6)	(2.1)
TC								
BL, mg/dL	271	267	265	268	267	268	261	263
Ls mean %	-2.5	-22.5***	-28.1***	-31.1***	-34.4***	-38.4***	-45.1***	-46.8***
change (SE)	(1.4)	(2.3)	(2.2)	(2.1)	(2.1)	(2.1)	(1.4)	(1.7)
HDL-C								
BL, mg/dL	53	55	49	53	50	51	52	51
Ls mean %	3.2	9.4	8.8	13.7*	14.6*	8.2	10.1	14.1**
change (SE)	(2.1)	(3.5)	(3.3)	(3.2)	(3.2)	(3.2)	(2.0)	(2.6)
TG								
BL, mg/dL	122	116	133	121	135	134	117	119
Ls mean %	-1.9	-17.0	-11.6	-34.2**	-8.9	-21.9	-27.4**	-24.6*
change (SE)	(4.8)	(7.8)	(7.6)	(7.2)	(7.2)	(7.2)	(4.5)	(5.8)
NonHDL-C								
BL, mg/dL	218	212	216	215	217	217	209	212
Ls mean %	-3.7	-30.9***	-36.4***	-42.0***	-45.5***	-49.4***	-59.0***	-60.8***
change (SE)	(1.6)	(2.6)	(2.5)	(2.4)	(2.4)	(2.4)	(1.5)	(1.9)
ApoB								
BL, mg/dL	140	132	135	137	143	136	134	139
Lsmean %	-2.3	-25.9***	-33.0***	-36.6***	-40.5***	-44.9***	-53.6***	-55.2***
change (SE)	(1.6)	(2.6)	(2.6)	(2.4)	(2.5)	(2.4)	(1.5)	(2.0)
ApoA-I								
BL, mg/dL	145	140	134	140	135	137	141	141
Lsmean %	3.3	6.1	7.6	6.9	6.5	7.5	1.4	7.0
change (SE)	(2.4)	(3.8)	(3.7)	(3.5)	(3.5)	(3.5)	(2.2)	(2.9)

Table 5 ISE

Data derived from tables on pages A63, A66, A69, A72, A84, A87, A101, A597 to A604 in Appendix A.

[a] Main analysis of LOCF data from the ITT population.

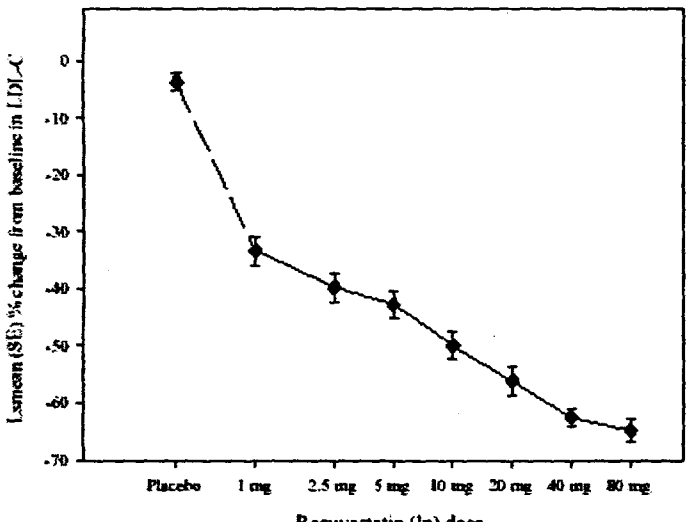
* $p<0.05$ versus placebo; ** $p<0.01$ versus placebo; *** $p<0.001$ versus placebo.

BL = baseline; N = All subjects in ITT population; SE = standard error.

Rosuvastatin was effective at producing a significant reduction in the % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol and ApoB at doses from 1 mg to 80 mg compared to placebo. The % changes from baseline in LDL-cholesterol ranged from 1 mg (-33%) to 80 mg (-65%). While increases in mean % change from baseline of HDL-cholesterol and decreases in mean % change from baseline of triglycerides were seen for doses from 1 mg to 80 mg there was no dose-response relationship and the values were not statistically significant at all doses. However, patients with low HDL-cholesterol at trial entry, <34 mg/dl, had greater increases in HDL-cholesterol on 5 to 10 mg of rosuvastatin than patients with HDL ≥ 35mg/dl (15.6% vs. 7.3%). Similarly, patients with Type IIB dyslipidemia (TG> 200mg/dl at baseline) had greater mean decreases from baseline in TG than patients with Type IIA (TG<200 mg/dl at baseline), -23.1% vs. -11.8%. An insufficient number of African Americans (N=0), Hispanics (N=0) and Asians (N=2) were included in these studies to independently confirm the efficacy in these subpopulations.

Figure 1 % LDL-C reduction by dose of rosuvastatin in Type IIA/IIB dyslipidemia:

Trials 8 and 23 pooled (Figure 1 ISE)



Data derived from tables on pages A63, A597 to A604 in Appendix A. The natural log scale (ln) was applied to the dose axis only. The percent change from baseline axis is linear. Main analysis on LOCF data from the ITT population. N = All subjects in ITT population, as follows: placebo, N = 31, rosuvastatin doses: 1.0 mg, N = 14; 2.5 mg, N = 15; 5 mg, N = 18; 10 mg, N = 17; 20 mg, N = 17; 40 mg, N = 34; and 80 mg, N = 31.

While the % change from baseline in LDL-cholesterol appears dose dependent, it is not linear when plotted with respect to the natural log of the dose as seen in Figure 1 above. Most of the effect at LDL-cholesterol lowering is seen with just 1 mg of rosuvastatin (-33%). At the highest doses the curve flattens out and there is no clear difference between the effect seen at 40 and 80 mg. When looking specifically at Trial 23, in which the 40 and 80 mg doses were directly compared,

the difference in the mean % change from baseline in LDL-cholesterol between these two doses was only -0.9%.

In addition to Trials 8 and 23, Trial 24, a 12-week study, also compared efficacy of rosuvastatin (5 and 10 mg) to placebo. The results from this study were consistent with the two earlier trials.

Trials 25, 26, 27, 28 and 33, ranging in length from 6 to 24 weeks, were all designed with active comparators as controls. Rosuvastatin was effective at lowering LDL-cholesterol in all of these trials. However, without a placebo group it is not possible to compare these results to the earlier trials. While the sponsor went to great effort to compare the efficacy of rosuvastatin to all currently marketed statins, it is not the purpose of this review to make relative efficacy claims between statins. The reader is referred to Joy Mele's statistical review for an analysis of the comparative efficacy data.

Trials 26 and 28 were designed to compare doses of 5 and 10 mg of rosuvastatin at 12 weeks and then to titrate the dose as needed up to 80 mg to achieve each patient's NCEP II target LDL-cholesterol.

Table 5 Percentage of Patients Reaching NCEP Target LDL-cholesterol at 52 Weeks

Dose needed to get NCEP goal	Trial 26				Trial 28				Trials 26 and 28 (pooled data)			
	Start Dose 5 mg		Start Dose 10 mg		Start Dose 5 mg		Start Dose 10 mg		Start Dose 5 mg		Start Dose 10 mg	
	N=121	%	N=106	%	N=101	%	N=96	%	N=222	%	N=202	%
5	83	69	-		66	65	-		149	67	-	
10	18	15	87	83	13	13	76	79	31	14	163	81
20	3	2	12	11	5	5	6	6	8	4	18	9
40	0	0	3	3	3	3	2	2	3	1	5	2
80	3	2	2	2	2	2	0	0	5	2	2	1
Didn't reach target	14	12	2	2	12	12	12	13	26	12	14	7

Data taken from Table E1.42.3 in ISE

5 and 10 mg daily doses of rosuvastatin are adequate for most patients (67 to 81%) to reach their NCEP LDL-cholesterol targets. Increasing the dose from 20 to 80 mg resulted in only an additional 3 to 4 % of patients reaching NCEP II goals. Significant safety issues at these higher doses of rosuvastatin (see Review of Safety 7.1.) are likely to out weigh this small increase in efficacy.

6.3.2 FAMILIAL AND NONFAMILIAL HYPERCHOLESTEROLEMIA
Rosuvastatin was studied in patients with primary hypercholesterolemia in randomized trials 30, 31, and 54.

Table 6

Trials Supporting the Efficacy of Rosuvastatin in Subjects with Familial (Heterozygous and Homozygous) and Nonfamilial Hypercholesterolemia

Trial No.	Design/principal location	N	Mean age Gender	Rosuva-statin dose (mg/day)	Comparator or combination dose (mg/day)	Baseline LDL-C (mg/dl)	Duration weeks	Time of 1° end-point %ΔLDL-C
30	Randomized, DB, active comparator, force-titration in subjects with heterozygous FH; Europe, USA,S Africa, Australia	623	48 y 342 m 281 f	20/40/80	Atorvastatin 20/40/80	>220<500	18	18 w
31	Randomized, open-label, combination in subjects with heterozygous FH or nonfamilial hypercholesterolemia; USA	153	55 y 85 m 68 f	40/80	Combination with cholestyramine 16 g	>190≤400	12	6 w[b]
54	Phase 1: open-label rosuvastatin; subjects with homozygous FH; Europe, USA,S Africa, Australia	44	29 y 8<18 y 26 m 18 f	20/40/80 open label		>500[a]	30	18 w

Table 32 ISE, Data derived from individual trial reports.
[a] Not relevant if subject met genetic or functional criteria for homozygous FH.
[b] In Trial 31, all subjects were treated with rosuvastatin 40 mg from baseline (Week -6) to Week 0 (pre-randomized treatment phase); following randomization, subjects were treated with their randomized treatment from Week 0 to Week 6; results were measured over the entire 12 week period.
DB = double-blind; FH = Familial hypercholesterolemia; N = total number of subjects randomized to treatment; f = female; m = male; y = years; w = weeks.

HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA
Trial 30 was a multi-center, double blind, parallel group, randomized trial comparing rosuvastatin to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia (baseline fasting LDL-cholesterol >220 and < 500 mg/dl and baseline fasting TG < 400 mg/dl). Patients were started on 20 mg of rosuvastatin or atorvastatin and then force titrated at 6-week intervals to 40 and finally 80mg of the same drug. Trials included men and women 18 to 70 years of age. Patients were planned to be randomized in a 3:1 ratio to rosuvastatin (N=436) and atorvastatin (N=187), but because of an error in the initial randomization scheme more patients than expected were randomized to the atorvastatin arm. The primary endpoint was percentage change from baseline to week 18 in LDL-cholesterol. The secondary endpoints were percent change from baseline to week 18 for HDL-cholesterol, TG, total cholesterol, ApoA-I, ApoA-II, ApoB, and C-reactive protein. The mean baseline LDL-cholesterol values were 292.5 and 287.6 mg/dl for the rosuvastatin and atorvastatin groups, respectively.

Table 7

Summary of Changes of Efficacy Parameters at Week 18 (ITT population) in study 4522IL/0030

Efficacy endpoint	Rosuvastatin	Atorvastatin
	20/40/80 mg	20/40/80 mg
Ls mean of percentage change from baseline to Week 18 in lipids and lipid ratios		
LDL-C	-57.88[a,c]	-50.41
TC	-46.35[a]	-42.13
HDL-C	12.36[a]	2.91
TG	-27.82[ns]	-31.60
ApoB	-50.21[a]	-44.44
ApoA-I	5.86[a]	-2.33
Percentage subjects reaching NCEP or EAS targets for LDL-C levels at Week 18[b]		
NCEP, overall	60.5	46.0
NCEP, high-risk	23.9	3.2
EAS, overall	47.4	24.1
EAS, high-risk	47.5	24.2
Median percentage change from baseline to Week 18 in inflammatory marker (Observed data)		
CRP	-34.00	-33.33

[a] $p<0.001$ in favour of ZD4522 20/40/80 mg;

[ns] = not significant versus atorvastatin 20/40/80 mg ($p>0.050$).

[b] Prospective protocolled statistical analyses were not performed for achievement of NCEP and EAS targets.

[c] Primary efficacy endpoint. Ls mean = Least squares mean. Data from Table 38 Study 0030

Rosuvastatin was effective at producing statistically significant reductions in the mean % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol, ApoB and HDL-cholesterol in subjects with severe hypercholesterolemia (LDL-cholesterol > 220mg/dL) at daily doses of 20 to 80 mg compared to atorvastatin. Both treatments produced a decrease in triglycerides over this same dose range that was not statistically significant between treatments.

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FIGURE 2- Percent Change in LDL-Cholesterol in Patients with Heterozygous Familial Hypercholesterolemia (ITT) (Fig. 2 Study 4522IL/0030)

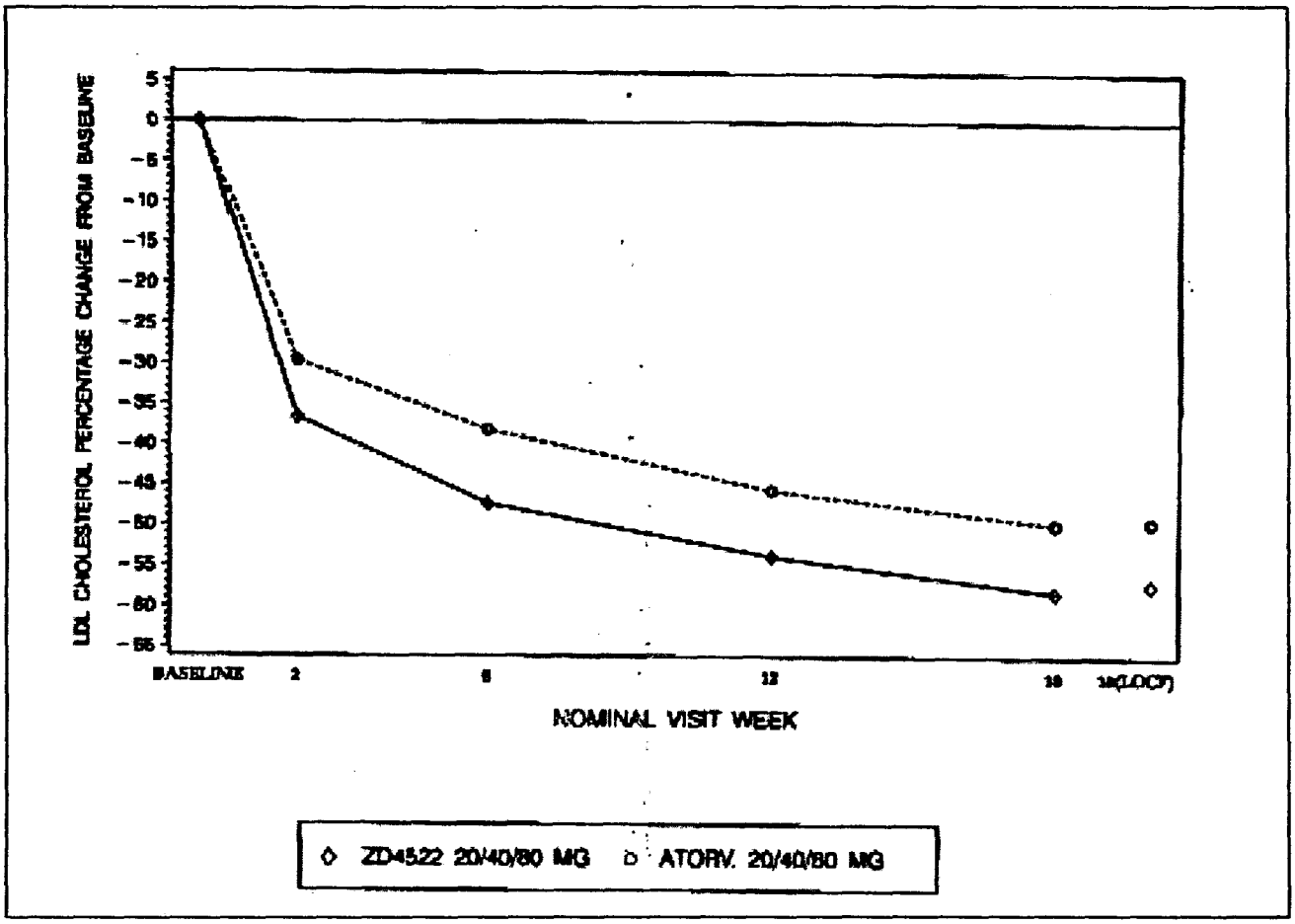

Table 8	Patients with Heterozygous Familial Hypercholesterolemia Treated with Rosuvastatin (ITT population)					
0 mg (0wks)	20mg (6wks)		40mg (12wks)		80mg (18wks)	
Baseline LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)
292	-47%	154	-54%	135	-58%	123
Data derived from Table T10.1.1						

The majority of the decrease in LDL-cholesterol was seen with 20 mg of rosuvastatin (wk 6). Titration from 20 to 40 mg provided an average 7% further reduction in LDL-cholesterol and an average 4% reduction with titration from 40 to 80 mg. It is this medical reviewer's opinion that these

small changes in LDL-cholesterol at the higher doses of rosuvastatin in this patient population do not outweigh the relative risks of rhabdomyolysis and renal disease seen at these higher doses in this NDA (see Safety Review 7.1.).

Trial 31 was a multi-center, open label, randomized trial comparing rosuvastatin in combination with cholestryamine in the treatment of patients with heterozygous familial hypercholesterolemia (baseline fasting LDL-cholesterol >190 and < 400 mg/dl and baseline fasting TG < 400 mg/dl). All patients were started on 40 mg of rosuvastatin for 6 weeks and then randomized to 80 mg of rosuvastatin with or without cholestyramine for another 6 weeks. Trials included men and women 18 to 70 years of age. The primary endpoint was percentage change from baseline to week 12 in LDL-cholesterol. The secondary endpoints were percent change from baseline to week 12 for HDL-cholesterol, TG, total cholesterol, ApoA-I, ApoB, C-reactive protein, interleukin-6 and E-selectin. The mean baseline LDL-cholesterol values were 257.4, 262.8 and 255.5 mg/dl for the rosuvastatin 40 mg, 80 mg, and 80mg + cholestyramine groups respectively.

Table 9 Summary of key efficacy findings (LOCF on ITT population)

	Pre-randomized to Week 0	Randomized treatment, Week 0 to Week 6		
Efficacy endpoint	ZD4522 40 mg[b]	ZD4522 80 mg[b]	ZD4522 80 mg + cholestyramine[b]	p-value[c]
	N = 153	N = 71	N = 76	
% change from baseline (Week –6) to Week 6 in lipids and lipid ratios				
	Mean (SD)	**Ls mean (SE)**	**Ls mean (SE)**	
LDL-C	–52.2 (13.0)	–56.35 (1.82)	–60.52 (1.75)	0.079
TC	–40.7 (9.6)	–43.31 (1.52)	–45.82 (1.47)	0.204
HDL-C	12.9 (12.5)	11.28 (2.06)	10.29 (1.98)	0.710
TG	–30.1 (18.6)	–23.31 (2.92)	–26.04 (2.80)	0.470
ApoB	–43.6 (11.6)	–46.91 (1.91)	–47.72 (1.83)	0.746
ApoA-I	9.0 (14.3)	8.31 (2.04)	9.97 (1.95)	0.532
Median % change from baseline (Week –6) to Week 6 in inflammatory markers				
C-reactive protein	NA	–42.22	–48.00	NA
Interleukin-6	NA	6.44	11.93	NA
E-selectin	NA	–3.25	–2.45	NA

Data derived from Tables T10.1, T10.4, T11.1, T11.4, T12.1, T12.4, T13.1, T13.4, T14.1, T14.4, T15.1, T15.4, T16.1, T16.4, T17.1, T17.4, T18.1, T18.4, T19.1, T19.4, T20.3, T21.3, and T22.3

[b] The main analyses (change from Week –6 to Week 6) is on the LOCF from the ITT population; summary statistics on the pre-randomized period (Week –6 to Week 0) are on observed data from the all treated population.

[c] p-value obtained from pair wise t-tests using least square means and mean square error from the ANOVA model.

Ls mean = Least squares mean; SD = Standard deviation; SE = Standard error.

Rosuvastatin (80 mg) in combination with cholestyramine (16g) in subjects with severe hypercholesterolemia appeared to be more effective at lowering LDL-cholesterol than rosuvastatin (80 mg) monotherapy, but the difference was not statistically significant p=0.079.

FIGURE 3- Percent Change in LDL-Cholesterol in Patients with Heterozygous Familial Hypercholesterolemia (ITT) at 0 weeks, 6 weeks (40 mg rosuvastatin), and 12 weeks (80 mg rosuvastatin ± cholestyramine) (Fig. 2 Study 4522IL/0031)

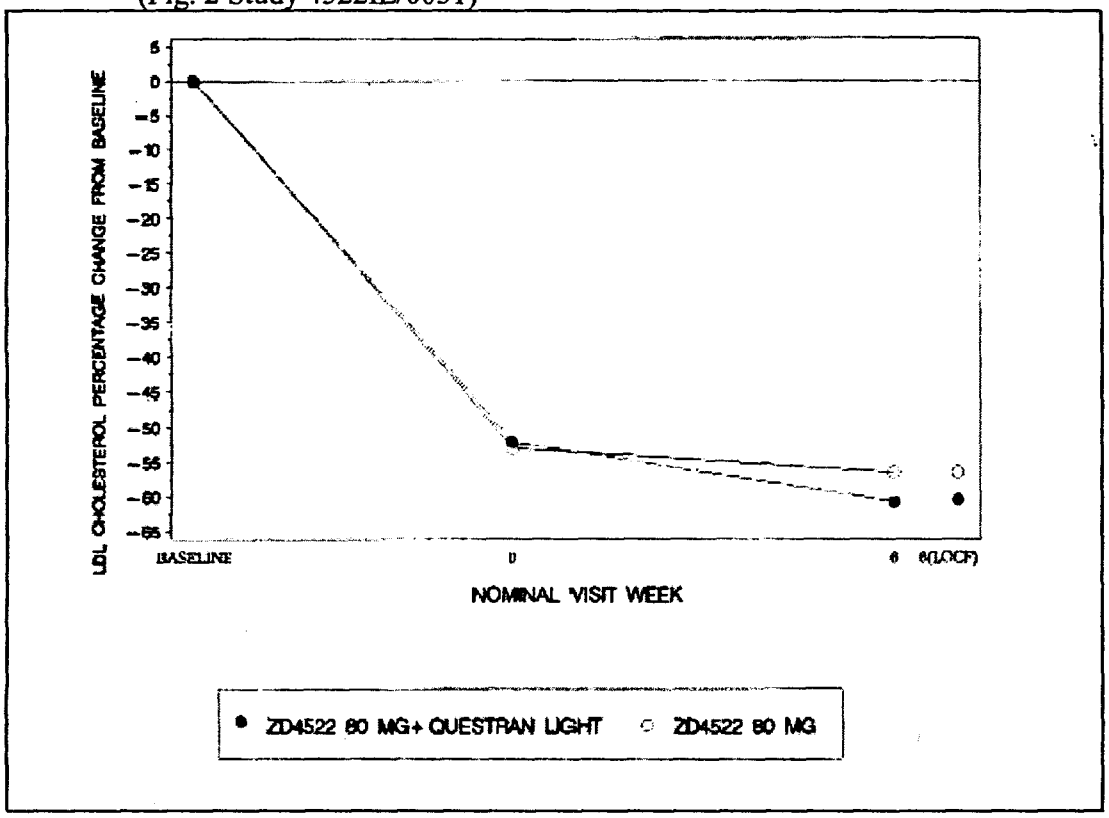

Table 10
Patients with Heterozygous Familial Hypercholesterolemia Treated with Rosuvastatin (ITT population) ± Cholestyramine

0 mg (0wks)	40mg (6wks)		80mg (12wks)		80mg + Cholestyramine (12wks)	
Baseline LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)
257	-52%	125	-56%	116	-61%	102
Data derived from Table T10.2.1 to T 10.3						

The majority of the decrease in LDL-cholesterol was seen with 40 mg of rosuvastatin at week 6. The smaller decreases in LDL-cholesterol between 40 mg of rosuvastatin (wk 6), and 80 mg of rosuvastatin (wk12), →4%

and 80 mg of rosuvastatin + cholestyramine (wk12), →9% are probably of questionable clinical significance. Both studies 30 and 31 show that there is only a small benefit (4%) in terms of LDL-cholesterol lowering in titrating patients with heterozygous familial hypercholesterolemia from 40 to 80 mg of rosuvastatin.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Trial 54 was a multi-center trial with an open label initial phase with a forced titration to 80 mg of rosuvastatin over 18 weeks, followed by a double blind, crossover, randomized phase comparing 80 mg of rosuvastatin to 80 mg of atorvastatin during an additional 12 week period. Only the open label phase of the trial was completed and included in this submission. 44 subjects with homozygous familial hypercholesterolemia (baseline fasting LDL-cholesterol >500 mg/dl and baseline fasting TG < 600 mg/dl) were randomized, including men and women 10 to 63 years of age. Eight subjects were < 18 years of age. The primary endpoint was percentage change from baseline to week 18 in LDL-cholesterol. The secondary endpoints were percent change from baseline to week 18 for HDL-cholesterol, TG, total cholesterol, ApoA-I, ApoB, Lp (a), C-reactive protein, interleukin-6 and E-selectin. The mean baseline LDL-cholesterol value was 515 mg/dl for all patients (516 mg/dl for receptor defective and 530 mg/dl for receptor unknown).

Table 11

Summary of key efficacy findings for the first 18 weeks of treatment; forced-titration period (LOCF on ITT population)

Efficacy variable	ZD4522 20/40/80 mg		
	Overall	Receptor defective	Receptor unknown
	(N = 42)	(N = 22)	(N = 16)
Mean of percentage change from baseline to Week 18 in lipids, lipid ratios, and lipoproteins (95% CI)			
LDL-C	-21.40 (-28.12, -14.67)	-22.17 (-30.55, -13.79)	-24.85 (-33.60, -16.11)
TC	-19.95 (-25.51, -14.40)	-19.89 (-27.69, -12.10)	-22.72 (-30.16, -15.29)
HDL-C	3.07 (-3.45, 9.60)	2.08 (-5.49, 9.64)	9.98 (-1.68, 21.64)
TG	3.28 (-11.31, 17.87)	3.60 (-14.61, 21.81)	5.17 (-24.36, 34.70)
ApoB	-20.0 (-25.9, -14.0)	ND	ND
ApoA-I	5.2 (-0.6, 11.1)	ND	ND
Lp(a)	28.5 (-2.9, 59.9)	ND	ND
Median of percentage change from baseline to Week 18[a] in inflammatory markers (min, max)			
CRP	-50.0 (-99, 9300)	ND	ND
IL-6	-15.26 (-59.8, 40.4)	ND	ND
E-Selectin	-15.26 (-59.8, 40.4)	ND	ND

[a] Analysis of observed data. 95% CI, = 95% Confidence Interval. ND = not done. Table 40 Study 4522IL/0054

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline LDL-cholesterol, total cholesterol, and ApoB and in subjects with homozygous familial hypercholesterolemia at doses from 20 mg to 80 mg. Changes in HDL-cholesterol and triglycerides were variable.

FIGURE 4- Percent Change in LDL-Cholesterol in Patients with Homozygous Familial Hypercholesterolemia (ITT) at 6 weeks (20mg), 12 weeks (40 mg) and 18 weeks (80 mg) of rosuvastatin (Fig. 3 Study 4522IL/0054)

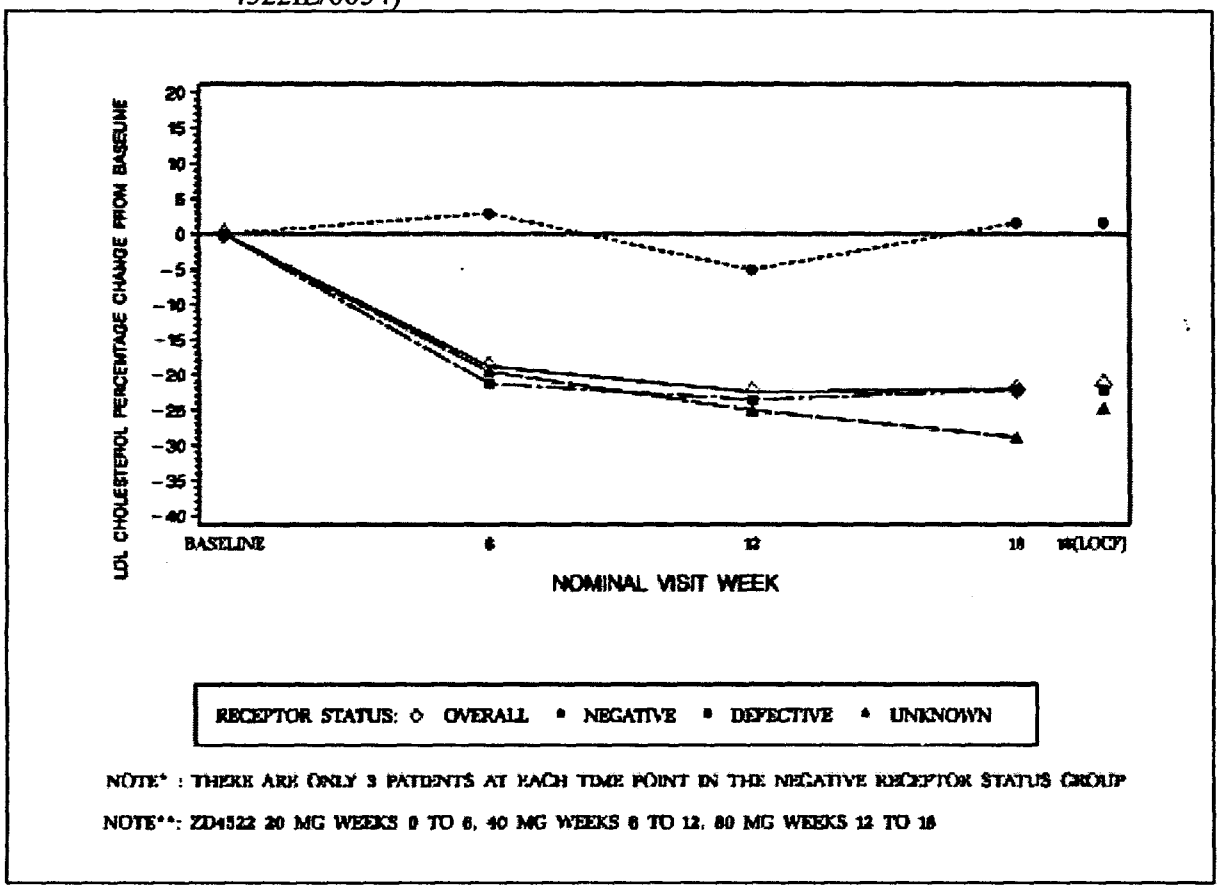

Table 12 All Patients with Homozygous Familial Hypercholesterolemia Treated with Rosuvastatin (ITT population)						
0 mg (0wks)	20mg (6wks)		40mg (12wks)		80mg (18wks)	
Baseline LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)
515	-19%	416	-23%	409	-22%	403
Data derived from Table T10.2.1 to T10.1.1						

The majority of the decrease in LDL-cholesterol was seen with 20 mg of rosuvastatin at week 6. In this medical reviewer's opinion the smaller decreases in LDL-cholesterol of 3 to 4% at 40 mg and 80 mg of rosuvastatin are clinically insignificant in patients with LDL levels of > 400 mg/dl. There is little clinical benefit to be gained in titrating patients with homozygous familial hypercholesterolemia above 20 mg of rosuvastatin.

6.3.3 HYPERTRIGLYCERIDEMIA in PATIENTS with FREDRICKSON TYPE IIB and IV DYSLIPIDEMIA

Rosuvastatin was studied in patients with Fredrickson Type IIb and IV dyslipidemia in randomized trials 29, 35, and 36.

Table 13 Trials Supporting the Efficacy of Rosuvastatin in Subjects with Fredrickson Type IIb or IV Dyslipidemia

Trial No.	Design/Principal location	N[a]	Mean age/ Gender	Rosuvastatin dose (mg/day)	Comparator/ Combination dose (mg/day)	Baseline lipids (mg/dl)	1° end-point [b]
29	Randomized, force-titration in subjects with Type IIB or IV dyslipidemia in comparison and combination; USA	270 162 IIB 101 IV	56 y 194 m 76 f	10/20/40	Niacin (extended-release) 0.5/1.0/1.5/2.0 g	TG: 200-800 TC: ≥200 HDL-C: <45 ApoB ≥110	ΔLDL-C(%) at 24 w
35	Randomized, DB, placebo-controlled, dose ranging in subjects with Type IIB or IV dyslipidemia; USA, Canada	156 65 IIb 88 IV	56 y 94 m 62 f	5/10/20/40/80	Placebo	TG: 300-800[c]	ΔTG (%) at 6 w
36	Randomized, 6 week DB placebo-controlled; subsequent 18 week open-label force-titration, comparison and combination, in Type 2 DM Type IIB or IV dyslipidemia Europe	216 144 IIB 62 IV	60 y 110 m 106 f	DB: 5/10 OL: 5/10/20/40	DB: Placebo OL: Fenofibrate 67 mg qd/bid/tid	TG: 200-800[d] TC: ≥200	ΔTG (%) at 24 w

Table 40 ISE, Data derived from Trial 29 Efficacy Summary Table E7.73.1; Trial 35, Efficacy Summary Table E7.73.2; Trial 36,
Efficacy Summary Table E7.73.3.

[a] N = total number of subjects randomized to treatment; the number of IIb + IV subjects were those in the ITT population.

[b] In this trial grouping, the trial duration was the same as the time point at primary endpoint measurement.

[c] The last 2 values of TG needed to be within 30% of each other.[d] The last 2 values of TG needed to be within 40% of each other.

DB = double-blind; OL = open label; w = weeks; y = years; f = female; m = male; qd/bid/tid =once/twice/three times daily.

Trial 35 was conducted using a 6-week, multi-center, double blind, fixed dose, and placebo controlled, parallel group trial design. After a 6-week dietary run in period, subjects were randomized to 5, 10, 20, 40 or 80 mg of rosuvastatin or placebo. Trials included men and women 18 to 70 years of age. Subjects had fasting triglyceride levels of >300 and < 800 mg/dl. Trial medication was given once daily 3 hours after the evening meal. A total of 156 patients were randomized into treatment groups of 23 to 27 subjects.

The primary endpoint was percentage change from baseline to week 6 in TG. The secondary endpoints were percent change from baseline to week 6 for LDL-cholesterol, HDL-cholesterol, total cholesterol, ApoA-I, ApoA-II, Lp(a), ApoB, and inflammatory markers activated factor XII , C-reactive protein, interleukin-6, and E-selectin. The mean baseline TG values ranged from 446 to 462 mg/dl for the rosuvastatin treatment groups but was slightly higher at 511 mg/dl in the placebo. The mean baseline LDL-cholesterol values ranged from 66 to 80 mg/dl for all treatment groups. The results are shown in Table 14 and Figure 5 below.

Table 14

Summary of Changes of Efficacy Parameters in Study 4522IL/0035

Efficacy endpoint	Ls mean of % change from baseline to Week 6					
	Placebo	ZD4522 5 mg	ZD4522 10 mg	ZD4522 20 mg	ZD4522 40 mg	ZD4522 80 mg
Lipids and lipid ratios						
TG	2.9	-18.1[a]	-37.0[a]	-36.8[a]	-40.0[a]	-39.5[a]
VLDL-TG	6.0	-10.8	-35.4[a]	-39.7[a]	-42.7[a]	-48.9[a]
LDL-TG	23.8	-5.7	-15.4	-4.5	-10.6	-16.5[a]
HDL-TG	-3.9	-3.7	-17.2	-18.8	-27.2[a]	-7.2
LDL-C	6.2	-27.5[a]	-40.1[a]	-33.6[a]	-39.0[a]	-45.2[a]
TC	2.5	-22.5[a]	-37.6[a]	-34.0[a]	-37.9[a]	-42.3[a]
HDL-C	-2.0	4.0	6.1[a]	18.3[a]	14.9[a]	10.0[a]
VLDL-C	5.5	-22.6[a]	-44.8[a]	-47.2[a]	-51.6[a]	-54.4[a]
ApoB	1.9	-21.4[a]	-35.9[a]	-33.0[a]	-37.1[a]	-44.0[a]
ApoA-I	1.2	0.9	1.5	6.7	6.0	3.0
ApoA-II	-1.4	2.1	-2.2	3.1	1.9	-2.6
Lp(a)	-8.6	29.1[a]	12.5	9.0	30.0[a]	1.1
Inflammatory markers[b]						
Activated factor XII	-0.2	1.2	-0.5	1.9	-0.6	-2.2
C-reactive protein	13.7	53.4	36.3	-6.0	-46.0	-30.2
Interleukin-6	0.3	-1.8	35.0	16.2	1.2	22.6
E-selectin	3.0	3.3	-9.2	-5.0	-2.7	-2.1

[a] $p<0.05$ versus placebo. Table 1 ZD4522/0035 summary [b] Hypothesis testing not performed for inflammatory markers.

FIGURE 5- Percent Change in Total TGs in Patients with Hypertriglyceridemia, Fredrickson Type IIB and IV (Fig. 3 Study 4522IL/0035).

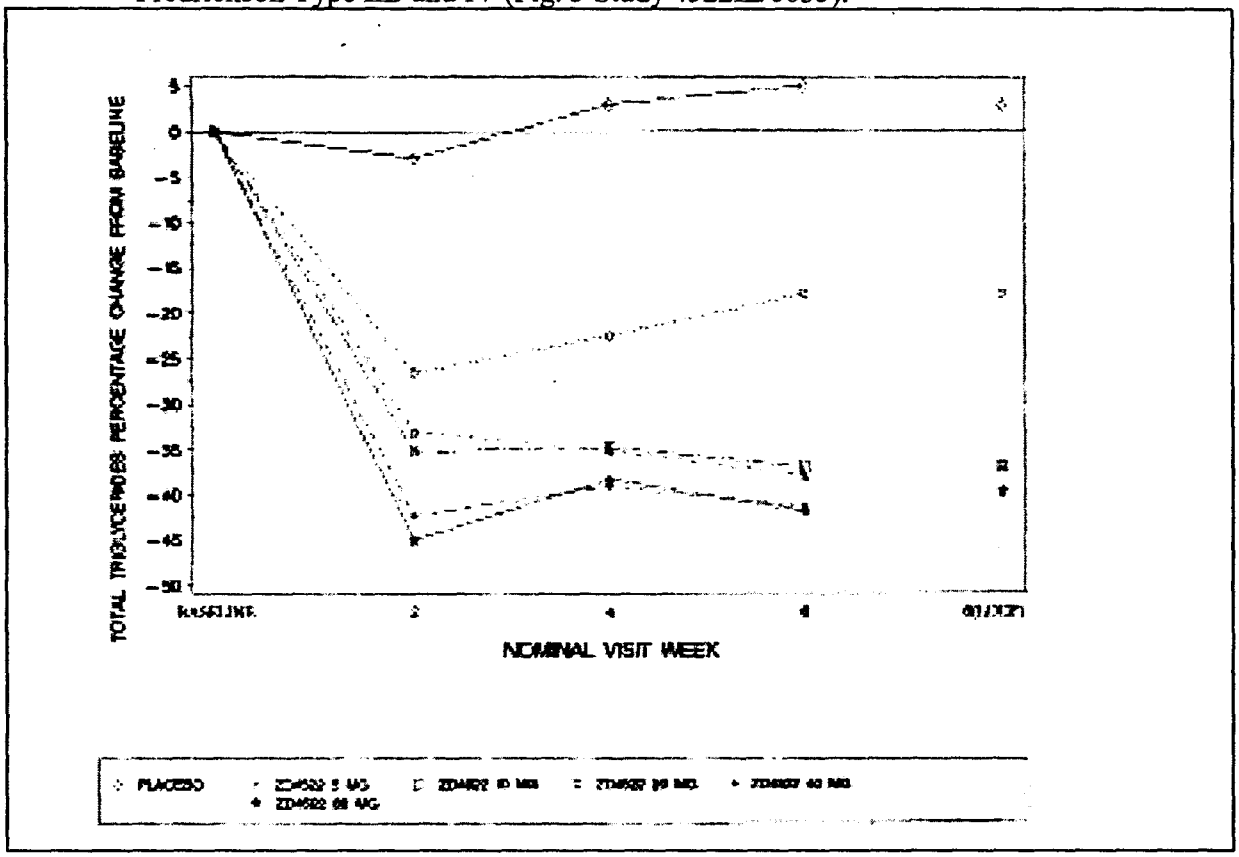

Table 15	Analysis of % Change from Baseline to Week 6 LOCF in total TG levels in study 4522IL/0035 [a]					
n	Placebo 26	ZD4522 25	ZD4522 23	ZD4522 27	ZD4522 25	ZD4522 27
		5 mg	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Baseline(mean, SD): mg/dl	511 (138)	462 (104)	447 (96)	446 (119)	471 (142)	448 (138)
Final (mean, SD):mg/dl	521 (222)	376 (140)	271 (65)	278 (114)	270 (81)	267 (96)
Ls mean of % change (SE)	2.9 (4.4)	-18.1 (4.5)	-37.0 (4.7)	-36.8 (4.3)	-40.0 (4.5)	-39.5 (4.3)
median	0.8	-20.6	-36.5	-37.0	-43.1	-46.2
Difference (%) relative to placebo	NA	**-21.0 (6.3)**	**-39.9 (6.4)**	**-39.6 (6.2)**	**-42.9 (6.3)**	**-42.4 (6.1)**
95% CI of difference	NA	-33.4, -8.6	-52.5, -27.3	-51.8, -27.5	-55.3, -30.5	-54.5, -30.2
p-value of difference	NA	0.001	<0.001	<0.001	<0.001	<0.001

Table 16 study 4522IL/0035. Data derived from Tables T10.1.1, T10.1.2, T10.3.1, and H1.1.1.
[a] Main analysis of last observation carried forward from the intent-to-treat population.
CI = Confidence interval; LOCF = last observation carried forward; ls mean = Least squares mean; NA = Not applicable; SD = Standard deviation; SE = Standard error.

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline triglycerides in subjects with Fredrickson

type IIB and IV dyslipidemia at doses from 5 to 80 mg compared to placebo. The mean dose response curve was flat at doses above 10 mg whereas the median dose-response curve was suggestive of a dose response relationship. These data suggest that a subset of patients were poor responders to higher doses.

The clinical significance of an18% to 40% decrease in triglyceride levels is not clear. The sponsor referenced several articles to suggest that a 20 to 30% decrease may be clinically meaningful (Bakker-Arkema et al., 1996, Faergman et al., 2000 and Ooi et al 1997). The meta-analysis by Hokanson and Austin suggests that serum triglycerides are a risk factor for cardiovascular disease independent of HDL-cholesterol. However, clinical trials have not been performed to quantify the percentage of triglyceride lowering which is necessary to result in a decrease in cardiovascular risk. Current NCEP guidelines recommends nonHDL cholesterol as a secondary target for patients with high triglycerides, > 200 mg/dl.

Trial 29 was set up to compare rosuvastatin, niacin and combination therapy with both for LDL-cholesterol and TG lowering. The study had a 24 week, multi-center, randomized, open-label, forced titration, parallel group trial design. After a 6-week dietary run in period, subjects were randomized into 4 different 24 week treatment periods. Treatment group A (rosuvastatin only group) was titrated from 10 to 20 to 40 mg of rosuvastatin. Treatment group B (niacin only group) was titrated from 0.5 to 1 to 1.5 to 2 g of niacin. Treatment group C was titrated from 0.5 to 1 g of niacin and from 0 to 10 to 20 to 40 mg of rosuvastatin. Treatment group D was titrated from 0.5 to 1 to 1.5 to 2 g of niacin and from 0 to 10 mg of rosuvastatin. Subjects were randomized in a ratio of 2:3:3:3. Trials included men and women 18 to 70 years of age. Subjects had fasting triglyceride levels of >200 and < 800 mg/dl. A total of 270 patients were randomized into treatment groups of 46 to 80 subjects. The primary endpoint was percentage change from baseline to week 24 in LDL-cholesterol. The secondary endpoints were percent change from baseline to week 24 for, TG, HDL-cholesterol, total cholesterol, ApoA-I, ApoA-II, Lp(a), ApoB, and activated factor XII. The mean baseline TG values ranged from 364 to 383 mg/dl for all treatment groups. The mean baseline LDL-cholesterol values ranged from 145 to 146 mg/dl for all treatment groups. The results are shown in Table 16.

Table 16

Summary of Changes in Efficacy Parameters in study 4522IL/0029

Efficacy endpoint	Ls mean of % change from baseline at Week 24			
	ZD4522 10/20/40 mg	Niacin 0.5/1/1.5/2 g	ZD4522 10/20/40 mg with niacin 0.5/1 g	ZD4522 10 mg with niacin 0.5/1/1.5/2 g
Lipids and lipid ratios[a]				
LDL-C	-47.5	-0.1[b]	-42.4	-35.5[b]
TC	-40.7	-7.2[b]	-37.5	-29.1[b]
HDL-C	**10.6**	**12.3**	**16.7**	**23.7**[b]
HDL-TG	-11.1	-4.9	-8.9	-15.1
TG	**-32.6**	**-20.9**	**-38.6**	**-33.9**
LDL-TG	-23.4	36.7[b]	-30.2	-7.8
VLDL-TG	-43.5	-23.1	-43.6	-35.4
VLDL-C	-51.0	-22.0[b]	-46.6	-38.4
ApoB	-42.4	-8.9[b]	-41.7	-33.7[b]
ApoA-I	4.7	7.0	6.2	10.6[b]
ApoA-II	-2.4	-4.2	-5.7	0.5
Lp(a)	6.5	-19.8[b]	-17.5[b]	-20.2[b]
Activated factor XII[c]				
Activated factor XII	2.7	-2.5	3.6	1.0

[a] Main analysis of LOCF from the ITT population. Data from Table I summary of ZD4522/ 0029
[b] $p<0.017$ versus ZD4522 40 mg.
[c] Observed data from the ITT population. Hypothesis testing not performed for activated factor XII.

Rosuvastatin in combination with niacin in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin. Rosuvastatin in combination with niacin appeared to be more effective at lowering triglycerides than monotherapy with either drug alone but it was not statistically significant.

Trial 36 was set up as a 24-week, multi-center, 4-group trial to compare monotherapy with rosuvastatin, or niacin to combination therapy with both for TG lowering. After a 6-week dietary run in period, subjects were randomized under double blind conditions for 6 weeks to receive a fixed dose of 5, or 10 mg of rosuvastatin or placebo, in a 1:1:2 ratio. The subsequent 18-week period was an open label force titration of fenofibrate or rosuvastatin at 6 weeks intervals. The final groups consisted of patients on: 40 mg of rosuvastatin alone, 201 mg of fenofibrate alone, the combination of 5 mg of rosuvastatin and 201 mg of fenofibrate, and the combination of 10 mg of rosuvastatin and 201 mg of fenofibrate. Trials included type 2 diabetic men and women 18 to 64 years of age. Subjects had fasting triglyceride levels of >200 and < 800 mg/dl. A total of 216 patients were randomized into treatment groups of 49 to 60 subjects. The primary endpoint was percentage change from baseline to week 24 in TG. The secondary endpoints were percent change from baseline to week 24 for LDL-cholesterol, HDL-cholesterol, total cholesterol, ApoA-I, ApoA-II,

ApoB, and Lp(a). The mean baseline TG values ranged from 307 to 369 mg/dl for all treatment groups. The mean baseline LDL-cholesterol values ranged from 142 to 150 mg/dl for all treatment groups. The results are shown in Table 17.

Table 17	**Summary of Changes in Efficacy Parameters at Weeks 24 in study 4522IL/0036 (LOCF on ITT population)**			
(6wk double blind phase)	**Placebo**	**Placebo**	**ZD4522 5 mg +**	**ZD4522 10 mg +**
(18 wk open label phase)	**Placebo ZD4522-10/20/40 mg** N= 53	**Placebo Fenofibrate 201mg** N=49	**ZD4522 5 mg + Fenofibrate 201mg** N=60	**ZD4522 10 mg + Fenofibrate 201mg** N=54
Efficacy end-point	**lsmean of % change from baseline to Week 24 in key lipids and lipid ratios**			
TG	**-30.25**	**-33.55**	**-40.88**	**-47.11[a]**
LDL-C	-46.69	0.70[a]	-34.06[a]	-42.16
TC	-36.58	-7.49[a]	-30.97	-36.26
HDL-C	**6.42**	**9.24**	**10.79**	**11.72**
VLDL-C	-43.56	-30.09	-46.81	-44.16
VLDL-TG	-31.93	-14.68	-32.46	-41.53
ApoA-I	2.71	5.02	4.72	5.41
ApoB	-41.38	-7.55[a]	-34.98	-40.21
Lp(a)	67.30	41.50	22.86	39.22

Table 38 Study 4522IL/0036

[a] $p \leq 0.017$ versus ZD4522 10/20/40 mg. A threshold for statistical significance of $p \leq 0.017$ was used at Weeks 12, 18 and 24 in order to control for multiple comparisons.

Feno = fenofibrate; ls mean = Least squares mean; NA = results not available due to inadequate samples

Rosuvastatin in combination with fenofibrate in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at decreasing triglycerides than monotherapy with rosuvastatin alone. Rosuvastatin in combination with fenofibrate appeared to be more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin alone but it was not statistically significant.

6.4. Efficacy Conclusions

Rosuvastatin was effective at producing significant reductions in the % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol and ApoB in subjects with Fredrickson type IIA and IIB dyslipidemia at daily doses from 1 mg to 80 mg compared to placebo. The % changes from baseline in LDL-cholesterol ranged from 1 mg (-33%) to 80 mg (-65%). Most patients reached NCEP target LDL-cholesterol on 5 or 10 mg of rosuvastatin (67 and 81%, respectively). Increasing the daily dose from 20 to 80 mg resulted in only an additional 3 to 4 % of patients reaching NCEP goals. While increases in mean % change from baseline of HDL-cholesterol and decreases in mean % change from baseline of triglycerides were seen for daily doses from 1 mg to 80 mg there was no dose-response relationship and the values were not statistically significant

at all doses. However, patients with low HDL-cholesterol at trial entry, <34 mg/dl, had greater increases in HDL-cholesterol on 5 to 10 mg of rosuvastatin than patients with HDL ≥ 35mg/dl (15.6% vs. 7.3%). Similarly, patients with Type IIB dyslipidemia (TG> 200mg/dl at baseline) had greater mean decreases from baseline in TG than patients with Type IIA (TG<200 mg/dl at baseline, -23.1% vs. -11.8%). An insufficient number of African Americans, Hispanics and Asians were included in these studies to independently confirm the efficacy in these subpopulations.

Rosuvastatin was effective at producing statistically significant reductions in the mean % change from baseline total cholesterol, LDL-cholesterol, nonHDL-cholesterol, ApoB and HDL-cholesterol in subjects with severe hypercholesterolemia (LDL-cholesterol > 220mg/dL) at daily doses of 20, 40 and 80 mg compared to atorvastatin. Both treatments produced a decrease in triglycerides over this same dose range that was not statistically significant between treatments.

Rosuvastatin in combination with cholestyramine (16g) in subjects with severe hypercholesterolemia (LDL-cholesterol > 190mg/dL) appeared to be more effective at lowering LDL-cholesterol than rosuvastatin (80 mg) monotherapy, but the difference was not statistically significant.

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline total cholesterol, LDL-cholesterol, nonHDL-cholesterol, and ApoB and in subjects with homozygous familial hypercholesterolemia (mean baseline LDL-cholesterol of 515 ± 115 mg/dl) at daily doses of 20, 40 to 80 mg, but there was little additional benefit for daily doses greater than 20 mg. All three doses provided similar mean reductions in LDL-cholesterol from baseline (-20%, -24%, and –22%, respectively). Joy Mele's statistical review shows that approximately 30% of patients titrated to doses higher than 20 mg did achieve an additional 6% lowering in LDL-cholesterol, which corresponds to an additional decrease of about 30 mg/dl. It is this medical reviewer's opinion that these additional small decreases in LDL-cholesterol are unlikely to have much clinical impact in these patients whose mean LDL-cholesterol are still > 400 mg/dl. Changes in HDL-cholesterol and triglycerides were variable.

Rosuvastatin was effective at producing a significant reduction in the mean % change from baseline triglycerides in subjects with Fredrickson type IIB and IV dyslipidemia at daily doses from 5 mg to 80 mg compared to placebo. The mean dose response curve was flat at doses above 10 mg whereas the median dose-response curve was suggestive of a dose

response relationship. These data suggest that a subset of patients were poor responders to higher doses.

Rosuvastatin in combination with niacin in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin. Rosuvastatin in combination with niacin appeared to be more effective at lowering triglycerides than monotherapy with either drug alone but it was not statistically significant.

Rosuvastatin in combination with fenofibrate in subjects with Fredrickson type IIB and IV dyslipidemia was statistically more effective at decreasing triglycerides than monotherapy with rosuvastatin. Rosuvastatin in combination with fenofibrate appeared to be more effective at increasing HDL-cholesterol than monotherapy with rosuvastatin alone but it was not statistically significant.

Rosuvastatin was effective at lowering LDL-cholesterol in both men and women and in older and younger populations. The 10 mg daily dose appeared to be slightly more effective in women and in older patients (>65 y/o) than the 5 mg dose. Postmenopausal women showed the greatest response to the 10 mg dose. The difference was not robust enough to affect proposed dosing.

Rosuvastatin appears to be effective in Caucasians, Blacks, Hispanics, and Asians. However, the number of patients in the non-Caucasian subgroups is too small to draw any meaningful comparisons. A PK study in healthy Japanese volunteers showed an approximately two-fold increase in AUC and Cmax relative to Western counterparts.

Rosuvastatin showed a trend towards more LDL-cholesterol reduction with worsening renal function. In contrast, rosuvastatin showed a trend towards less LDL-cholesterol reduction with worsening liver function.