CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366/S-016

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW FOR JUPITER BACKGROUND PACKAGE

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-366

Drug Name: Crestor (rosuvastatin)

Indication(s): Hypercholesterolemia

Applicant: Astra-Zeneca

Date(s): Submitted 4/8/09
User fee date 2/8/10

Review Priority: Standard

Biometrics Division: Biometrics 2 (HFD-715)

Statistical Reviewer: David Hoberman, Ph.D..

Concurring Reviewers: J. Todd Sahlroot, Ph.D.

Medical Division: DMEP

Clinical Team: Mary Roberts, M.D.
Eric Colman, M.D.
Mary Parks, M.D.
Amy Egan, M.D.

Project Manager: Margaret Simoneau

TABLE OF CONTENTS

Background

The role of C-Reactive Protein (CRP) in the process of atherosclerosis has been examined over a number of years. Clinicians such as Dr. Paul Ridker and others have published articles estimating the association of CRP levels with the risk of major cardiovascular events (MCE) using extant databases. Several of these have shown evidence of a gradient of risk, particularly over the quintiles of CRP in large databases. In one study (AFCAPS/TexCAPS), Dr.Ridker observed that the incidence of events in the subgroup of "low LDL/ high CRP" (below/above the median with respect to each substance) 37/710 (5.2%) was similar to that in both high LDL subgroups. This finding generated the hypothesis that CRP may be an independent risk factor in a population with traditionally "low" LDL's. The JUPITER trial was designed to test whether patients without a history of coronary artery disease, with LDL < 130 mg/dL, and with CRP's greater than 2.0 mg/liter (roughly the median CRP in AFCAPS) would benefit from daily 20 mg rosuvastatin.

Design

JUPITER was an international study designed to detect a 25% reduction in risk of a major cardiac event (MCE), a composite endpoint consisting of the *first* experience of the following: fatal/non-fatal MI, fatal/non-fatal stroke, hospitalized unstable angina, or arterial vascularization. Secondary endpoints included total mortality, non-cardiovascular mortality, development of diabetes, development of deep vein thrombosis or pulmonary embolism, and bone fractures.

Subjects were randomized to placebo or 20 mg rosuvastatin. In order to achieve 90% power, the study required 514 events. Assuming an accrual period of one year and a mean follow-up of 3.5 years, the sponsor derived a sample size of 12,000, which was raised to 15,000 taking into account a possibly low placebo event rate and anticipated dropouts. A group sequential design incorporated 3 analyses with respective nominal alpha's of .003, .016, and .044. This plan corresponded to 37.5% information (195 events) at the first interim analysis, 75% information (390 events) at the second interim analysis, the final analysis at 520 events. The primary statistical analysis used the log rank test derived from the Cox proportional hazards model.

Results

After 89,846 subjects were screened 17,802 were randomized, 8901 to each treatment group. At the second interim analysis March 29, 2008, the DMC recommended termination of the study after 328 events (63% of total planned information). Approximately 7.5% of subjects in each group withdrew from the study, meaning that follow-up for MCE ceased and only vital status information was sought at the end of the trial.

The number patients randomized ranged from 14 in Uruguay to 4021 in the US, 2020 in Canada, 2873 in the UK and 2497 in South Africa.

There were 4 countries contributing at least 20 events: The US (152), Canada (66), UK (42) and South Africa (43), together accounting for 77% of the total number of MCE events. Poland, Russia, Denmark, Netherlands, Estonia, Israel, Germany, Argentina, Brazil, Mexico, Venezuela, Uruguay, Costa Rica, Guatemala, El Salvador, Panama, Colombia, Chile, Norway, Switzerland, Belgium, Bulgaria, and Romania contributed the rest.

Inclusion criteria were the following:

1. Written informed consent to participate in the study

2. Men aged 50 years and over; women aged 60 years and over (lowered from 55 years for men and 65 years for women per Amendment 4)

3. Fasting LDL-C value <130 mg/dL (3.36 mmol/L) at Screening Visit 1

4. hsCRP value ≥2.0 mg/L at Screening Visit 1

5. Triglycerides (TG) <500 mg/dL (5.6 mmol/L) at Screening Visit 1

Baseline characteristics of randomized patients were (according to the sponsor):

1) Males: 62%
2) mean age: 66
3) Whites: 71%
4) at most high school education: 59%
5) rarely/never exercise 50%, at least 2-3 times/week 38%
6) Current smokers: 16%
7) hypertension: 57%
8) family history of CHD: 11.5%
9) family history of stroke: 20.6%
10) FSG at least 100 mg/dL: 31.3%
11) Framingham Risk category: low 40.5%, Intermediate 50.5%, high 9%
12) mean BMI: 29
13) low HDL (< 40 mg/dL): 22.5%
14) metabolic syndrome: 41%

Baseline Lipid Levels mg/dL (mean of both groups)

	Mean	std
Total cholesterol	183	(24.4)
HDL-C	51	(15.3)
LDL-C	104	(18.7)
Apo A-I	165	(30.7)
Apo B	109	(21.4)
hsCRP	median 4.3 mg/L	

The following table displays the number and percentage of NCEP ATP III risk factors in each group.

	Rosuvastatin (N=8901)	Placebo (N=8901)	
1 risk factor (age only[a]), n (%)	2199 (24.7)	2080 (23.4)	4279 (24.0)
2 risk factors[b], n (%)	4373 (49.1)	4423 (49.7)	8796 (49.4)
3 risk factors[b], n (%)	1931 (21.7)	2017 (22.7)	3948 (22.2)
4 risk factors[b], n (%)	371 (4.2)	361 (4.1)	732 (4.1)
5 risk factors[b], n (%)	27 (0.3)	20 (0.2)	47 (0.3)

[a] All subjects were of increased age (inclusion criterion: men ≥50 years, women ≥60 years).

[b] Risk factors included are NCEP ATP III risk factors: age, smoking, hypertension, HDL <40 mg/dL (1.04 mmol/L), and family history of CHD

Note from the baseline table above that this subgroup comprises approximately 24% of the patients.

Primary Analysis Results

The median follow-up time to MCE or death on all randomized subjects was 2.0 years. After final adjudication of events, the sponsor reported that 2.8% (252) of the placebo subjects and 1.6% (142) of the rosuvastatin subjects had suffered a MCE. After 4 years of follow-up, the Kaplan-Meier estimates of the probability of a MCE event were 6.3% and 3.2%, respectively. The absolute treatment difference was 3.1% with a 95% confidence interval (1.7%, 4.5%). These estimates do not take into account the competing risk of non-cardiovascular deaths.

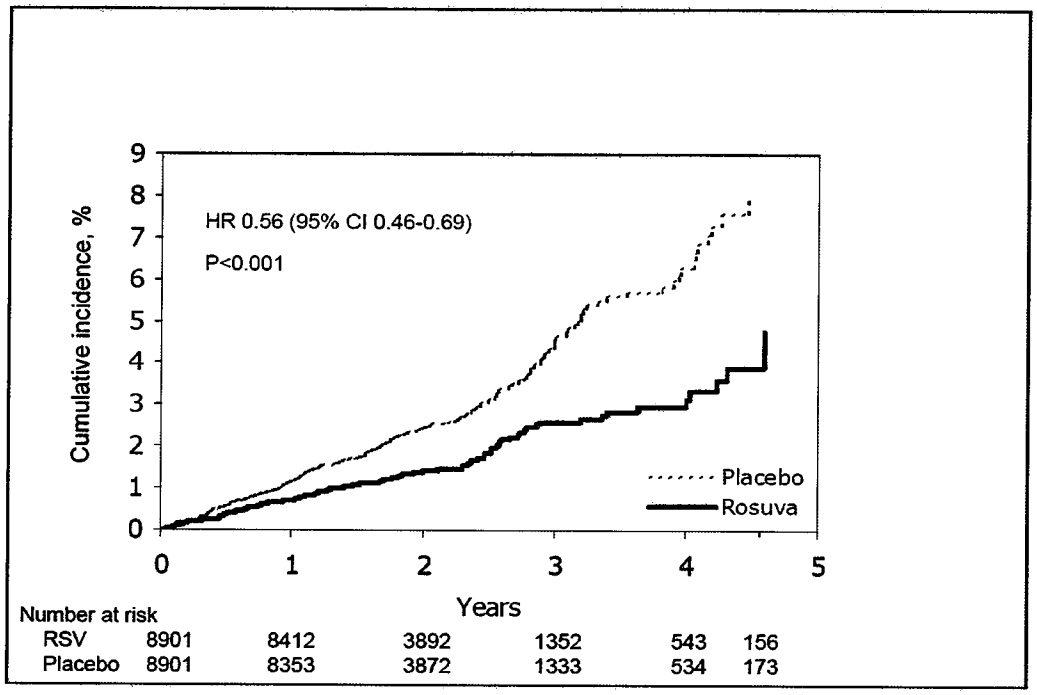
The primary analysis for time to first MCE yielded a hazard ratio of .56 with a 95% confidence interval of (.46, .69), p<.001. **Patients were supposed to have been excluded if they had at least one cardiovascular disease "equivalent". One of these was having a Framingham 10 score greater than 20. There were 1558 subjects who met this criterion but were nevertheless enrolled in the trial. These ineligible subjects accounted for 67 events, 29 in the Rouva group and 38 in the placebo group. Deleting these 1558 subjects produces a hazard ratio of .63 with a 95% confidence interval (.42, .68). In addition, there were 1294 subjects randomized who had baseline CRP's less than 2.0. However, these accounted for only a total of 22 events.**

The results for the primary analysis among the dominant four countries are displayed below:

Country	# events	hazard ratio	naïve 95% Confidence interval for hazard ratio
US	152	.63	.45-.89
Canada	66	.53	.31-.88
UK	42	.35	.17-.71
South Africa	43	.64	.34- 1.25

The figure below displays the sponsor's Kaplan-Meier plot for the primary MACE endpoint. Both the sponsor's residual analysis and log-log plots did not reveal substantial evidence of departure from proportional hazards.

Figure 4 **Kaplan-Meier plot for the primary composite endpoint**



Number Needed to Treat (NNT)

An alternative way to illustrate absolute treatment effect is to examine the number of subjects needed to treat in order to prevent one MCE event by different points in time. The following table displays estimates and confidence intervals for the NNT by year. They were calculated using Kaplan-Meier estimates and standard errors derived from SAS PROC LIFETEST.

		rosuva	PBO	NNT	95% CI
Survival probabilities	Year 1	.993	.988	200	(128, 460)
	Year 2	.986	.975	91	(65, 153)
	Year 3	.974	.954	50	(33, 100)
	Year 4	.968	.937	32	(22, 60)

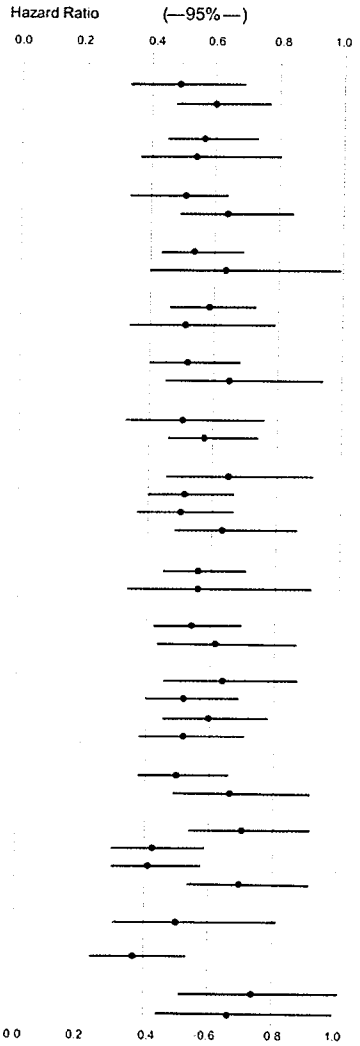
These estimates do not take into account the competing risk of non-cardiovascular deaths.

The Cox model adjusting for baseline covariates is displayed below.

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Variable Label
trt	1	0.59553	0.10580	31.6822	<.0001	1.814	TREATMENT GROUP
BMI	1	-0.04218	0.01151	13.4255	0.0002	0.959	BODY MASS INDEX (KG/M2) AT ENTRY
MS_BASE	1	0.16575	0.12225	1.8383	0.1752	1.180	METABOLIC SYNDROME AT BASELINE
B_HT	1	0.28129	0.11641	5.8386	0.0157	1.325	BASELINE HYPERTENSION GROUP
CHDRSK4	1	0.63166	0.13777	21.0212	<.0001	1.881	CIGARETTE SMOKING IN LAST MONTH
CHDRSK5	1	0.43346	0.13700	10.0104	0.0016	1.543	FAMILY HIST OF PREMATURE CHD/PVD
FRAM10	1	0.01803	0.01095	2.7118	0.0996	1.018	FRAMINGHAM 10YR RISK
AGER (YEARS)	1	0.05383	0.00821	43.0246	<.0001	1.055	AGE AT RANDOMIZATION
gen	1	-0.44117	0.15918	7.6812	0.0056	0.643	GENDER

Below is the sponsor's table of subgroup analyses.

Baseline characteristic	N of events[a] Rosuva 20 mg (N=8901) n (rate)[a]	Placebo (N=8901) n (rate)[a]	HR (95% CI)	P value for interaction
≤65 years at baseline	42 (4.9)	90 (10.3)	0.48 (0.33, 0.69)	0.338
>65 years at baseline	100 (9.9)	162 (16.6)	0.60 (0.47, 0.77)	
Male	103 (8.8)	182 (15.5)	0.57 (0.45, 0.73)	0.817
Female	39 (5.6)	70 (10.4)	0.54 (0.37, 0.80)	
Male <65 y, Female <75 y	55 (4.7)	120 (10.1)	0.46 (0.34, 0.64)	0.128
Male ≥65 y, Female ≥75 y	87 (12.9)	132 (20.1)	0.64 (0.49, 0.84)	
Caucasian	111 (7.8)	202 (14.4)	0.54 (0.43, 0.69)	0.561
Non-Caucasian	31 (7.0)	50 (11.1)	0.63 (0.40, 0.99)	
No	110 (6.9)	190 (12.1)	0.58 (0.46, 0.73)	0.644
Yes	32 (11.7)	62 (22.6)	0.51 (0.34, 0.79)	
≤30 kg/m²	94 (8.2)	179 (15.9)	0.52 (0.40, 0.67)	0.313
>30 kg/m²	47 (6.6)	73 (10.2)	0.65 (0.45, 0.94)	
< 40 mg/dL (1.0 mmol/L)	32 (7.6)	65 (15.3)	0.50 (0.33, 0.76)	0.512
≥40 mg/dL (1.0 mmol/L)	110 (7.7)	187 (13.1)	0.58 (0.46, 0.74)	
≤100 mg/dL (2.6 mmol/L)	55 (8.7)	86 (13.5)	0.65 (0.46, 0.91)	0.304
>100 mg/dL (2.6 mmol/L)	87 (7.1)	166 (13.7)	0.52 (0.40, 0.67)	
Above median[b]	68 (7.0)	138 (14.1)	0.50 (0.37, 0.67)	0.236
Below median[b]	74 (8.3)	114 (13.1)	0.64 (0.48, 0.86)	
<200 mg/dL (2.2 mmol/L)	117 (7.6)	208 (13.6)	0.56 (0.45, 0.71)	0.974
≥200 mg/dL (2.2 mmol/L)	25 (7.7)	44 (13.7)	0.56 (0.34, 0.91)	
Yes	89 (8.5)	166 (15.8)	0.54 (0.42, 0.70)	0.559
No	53 (6.6)	86 (10.8)	0.61 (0.43, 0.86)	
US	58 (10.7)	94 (16.9)	0.63 (0.45, 0.87)	0.395
Countries other than US	84 (6.4)	158 (12.2)	0.52 (0.40, 0.68)	
US or Canada	81 (9.7)	137 (16.3)	0.60 (0.45, 0.78)	0.536
Countries other than US/Canada	61 (6.0)	115 (11.4)	0.52 (0.38, 0.71)	
No	75 (6.9)	149 (14.0)	0.50 (0.38, 0.66)	0.167
Yes	67 (8.7)	102 (13.1)	0.67 (0.49, 0.91)	
above median[b]	89 (9.7)	128 (13.7)	0.71 (0.54, 0.92)	0.015
below median[b]	53 (5.6)	124 (13.5)	0.42 (0.30, 0.58)	
≤4 mg/L	50 (5.6)	119 (13.8)	0.41 (0.30, 0.57)	0.014
>4 mg/L	92 (9.5)	133 (13.5)	0.70 (0.54, 0.91)	
below median LDL and hsCRP	24 (5.6)	47 (11.3)	0.50 (0.30, 0.81)	
above median LDL and below median hsCRP	29 (5.7)	77 (15.3)	0.37 (0.24, 0.57)	
below median LDL and above median hsCRP	50 (10.9)	67 (14.7)	0.74 (0.51, 1.07)	
above median LDL and hsCRP	39 (8.5)	61 (12.8)	0.66 (0.44, 0.99)	0.094



CI Confidence interval; HDL-C High-density lipoprotein-cholesterol; HR Hazard ratio; hsCRP high sensitivity C-reactive protein; LDL-C Low-density lipoprotein-cholesterol; Rosuva Rosuvastatin; US United States; y Years.

[a] Number of events and event rate/1000-person years. The denominator is the time at risk on study in days, summed across the relevant subjects and divided by 365.25. The numerator is 1000 x number of events.

[b] Median baseline LDL-C was 108 mg/dL (2.80 mmol/L); median hsCRP was 4.25 mg/L.

Results are consistent between various subgroups with the possible exception of below and above median hsCRP. Not shown in this table is another sponsor's table in which the only noteworthy exception to consistency in the *post-hoc* subgroups is the fact that the hazard ratio among those with less than 2 NCEP ATP III risk factors was .9. The interaction p-value for comparing the treatment effect in this subgroup vs all other subjects was .032. This subgroup is the same as that with only the risk factor of age which is shared by all subjects in the study (See table of ATP risk factors above). The .9 hazard ratio reflects the very weak evidence of treatment benefit in this "no risk (other than age)" subgroup (33 events in the rosuvastatin group and 35 events in the placebo group).

In an article in the Journal of Thrombosis and Haemostasis [Vol 7 (suppl 1): 332-339], Dr. Ridker proposed a "age-only risk" subgroup which differs from the sponsor's in that Dr. Ridker's considered neither family history nor whether subjects were on hypertension medication. In both cases, a subject was "at risk" as hypertensive if the SBP was greater or equal to 140 or the DBP was greater or equal to 90. Thus, by including subjects who were taking hypertension medication or who had a family history of CHD in the "no risk" subgroup, Dr. Ridker's subgroup contains 6375 patients, whereas the sponsor's contains 4279. Dr. Ridker's subgroup produced a hazard ratio of .63 with 95% CI (0.44-0.92) with 45 events in the rosuvastatin group and 72 in the placebo group. Thus we find that Dr. Ridker's subgroup adds 12 MCE events to the placebo group and 37 MCE events to the rosuvastatin group, largely contributed by subjects who were taking hypertension medication.

MCE Components

The table below displays the number of *first* MCE events for each component.

First MCE	rosuvastatin	Placebo
Total	142	252
Cardiovascular death	29	37
Nonfatal MI	21	61
Non Fatal Stroke	30	57
Hospitalized Unstable Angina	15	27
Arterial revascularization	47	70

If a subject had more than 1 MCE on the same day, only 1 event is shown according to the following hierarchy: 1) unstable angina, 2) MI, 3) arterial revascularization, 4) non-fatal stroke, 5) cardiovascular death.

The incidence rates were 7.6 and 13.6 per 1000 patient years in the rosuvastatin and Placebo groups, respectively.

The sponsor's table below displays the statistical results for each component **including MCE events subsequent to the first**. Thus a subject can occur in more than one row. It does not count repeated events of the same kind.

	rosuvastatin	placebo		
	n %	n %	HR(95% CI)	p-value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51, 1.24)	0.315
Nonfatal stroke	30 (0.3)	58 (0.7)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (0.2)	62 (0.7)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54 (0.41, 0.72)	<0.001

Non-fatal Stroke, non-fatal MI, and arterial revascularization are statistically significant.

Lipid Lowering

Approximately 90% of subjects were available for lipid measurements at one year. After that point, data was scarce. The table below displays the sponsor's figures for **the mean percent change from baseline at one year** in each group:

	rosuvastatin	placebo	p-value
Total Cholesterol	-23.6%	-3.3%	< .001
HDL-C	7.6%	3.0%	<.001
LDL-C	-45.3%	5.4%	<.001
TG	-9.4%	6.8%	<.001
hsCRP	-12.9%	15.7%	<.001
hsCRP **median** change	-46.9%	-20.2%	

Secondary Endpoints

The results of the specified secondary endpoints subject to a sequential testing procedure are listed in the table below.

	rosuvastatin		placebo			
	n	%	n	%	HR(95% CI)	p-value
CV death/MI/stroke	83	(0.9)	158	(1.8)	0.52 (0.40, 0.68)	<0.001
Fatal or nonfatal MI	31	(0.3)	68	(0.8)	0.46 (0.30, 0.70)	<0.001
Fatal or nonfatal stroke	33	(0.4)	64	(0.7)	0.52 (0.34, 0.79)	0.002

Although Total Mortality (p=.021, HR=.80) was statistically significant at the .05 level when vital status data was used, it was neither a component of the MCE endpoint nor a secondary endpoint subject to Type I error control in the Statistical Analysis plan (SAP).

There were 198 deaths (2.2%) in the rosuvastatin arm and 247 deaths (2.8%) in the placebo arm. The Kaplan-Meier estimates at 4 years were 4.2% and 5.3% respectively, with an absolute risk difference of 1.1% and 95% confidence interval (0.3%, 1.9%).

Further inspection of the data shows that the Kaplan-Meier curves converge toward the end of the trial. At approximately 1600 days (4.4 years), the Kaplan-Meier estimate of the absolute difference in risk of death is 0.7% in favor of rouvastain with a 95% confidence interval (-0.4%, 1.8%). Thus, it is not clear whether or not rosuvastatin confers a total mortality advantage compared to placebo even though the logrank test appears to detect the separation of the survival curves up to over 4 years.

APPENDIX

The Log-Hazard as a Biased Estimator in the Planned Trial

When trials stop early at an interim analysis, the estimator used to measure treatment effect can be biased away from the 'true population' value. This section provides an asymptotic method for estimating the maximum bias using the estimated β-coefficient (βhat) derived from the Cox model with the treatment indicator as the only term. For simplicity, we regard the chances of stopping at the first look (190 events) as remote, so we deal only with stopping at the second look (390 events) or continuing to the end (520 events). In addition, we apply results that obtain using the central limit theorem with known variance to the asymptotic case of the log rank analysis as it applies to the Cox proportional hazards model with only the treatment 0-1 variable in the model. This is possible because standard results calculate the standard error of the log hazard ratio to be close to 2/sqrt(D), where D is the number of events at an interim analysis. Since this number has been fixed before the trial, we do not need to regard the standard error as a random variable.

The bias is calculated as the difference between two weighted conditional expectations. The first expectation is E[βhat| βhat exceeds the its critical value (z=2.41 on the normalized scale)] at the second look. The weight is the power or probability it will do so under alternatives to the null, in this case the null being β=0. The second expectation is E(βhat| βhat *does not* exceed the its critical value at the second look), i.e. the trial goes to completion. Its weight is 1-power. For the log hazard ratio, the difference between these two terms gives the bias *on the log scale.* Since 1) the plan anticipated 75% of the total information by the second analysis and 2) the fact that the standard error of the log hazard estimate at the second look would be .10, while that at the planned end of the trial would be very similar (.088), we expect any bias to be very modest. In fact, the maximum biased estimate of the hazard ratio itself is only 1% away from the 'true value' of the hazard ratio in the realistic range of 1.0 to 2.0.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID HOBERMAN
02/03/2010

JON T SAHLROOT
02/03/2010
concur