Statistical Review

NDA #: 21-198
Drug: Pravachol 10 mg Tablets OTC
Sponsor: Bristol-Myers Squibb
Indication: Reduction of LDL in an OTC population
Date of Submission: November 3, 1997
Statistical Reviewer: Joy Mele, M.S. (HFD-715)
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The sponsor has submitted the results of six double-blind controlled clinical studies (Table 1) and 1 open-label PK/PD study to support the efficacy and safety of pravastatin 10 mg for OTC use. In addition, the sponsor has submitted actual use studies and a label comprehension study to support their Rx to OTC switch request; these studies are being reviewed by the OTC Biometrics review group (HFD-725). All seven efficacy studies were submitted in the original pravastatin NDA (19-898) and therefore have been reviewed previously by FDA and are not reviewed in detail here. Only data for the first 2 studies listed (27201-2 and 27201-42) was available from the sponsor.

Table 1. Double-blind controlled efficacy/safety studies for Pravastatin 10mg

	Treatment groups (N)	Demographics	Duration	LDL[1] Results of 10 mg dose [2] Mean (SD)
27201-2	**PRAV 5mg BID (74)** PRAV 10mg BID (63) PRAV 20mg BID (68) PLA (101)	~75% male mean age 52 mean TC ~305	12 weeks	Baseline 236 (59) Week 8 %Change **–19%** (11) Week 12 %Change **–16%** (12)
27201-42	PRAV 5mg QD (26) **PRAV 10mg QD (26)** PRAV 20mg QD (26) PRAV 40mg QD (23) PLA (49)	~50% male mean age 54 mean TC ~296	8 weeks	Baseline 231 (43) Week 8 %Change **–22%** (15)
27201-89	**PRAV 10mg QD (73)** PLA (38)	Gender NA mean age 58 mean TC ~265	8 weeks	Baseline 187 (NA) Week 8 %Change **–18%** (NA)
Japanese #4	**PRAV 5mg BID (47)** PRAV 10mg BID (47) PLA (24)	~28% male med age ~55 mean TC ~286	8 weeks	Baseline 202 (48) Week 8 %Change **–24%** (NA)
Japanese #5	**PRAV 10mg QD (144)** Clinofibrate 200mg TID (140)	~34% male med age ~55 mean TC ~275	16 weeks	Baseline 191 (4.3?) Week 12 %Change **–22%** (NA)
Japanese #6	**PRAV 5mg BID (175)** Compound X (177)	~36% male med age ~55 mean TC ~281	16 weeks	Baseline 199 (3.9?) Week 12 %Change **–26%** (NA)

The sponsor defines the targeted OTC population as individuals with total cholesterol (TC) of 200 to 240 and with no history of heart disease (see Appendix 1, the back panel of the proposed OTC package which outlines the target OTC population). The sponsor claims that

1 LDL-C was calculated using the Friedewald formula. Blood samples were drawn after a 12-hour fast.
2 Results for the first 2 studies are reviewer's results; for remaining studies, sponsor's results are presented. Question marks indicate values reviewer considers questionable.

Keywords: Clinical studies, over-the-counter

subjects not at NCEP goal levels for TC (<200) and LDL (<130) will reach these levels through usage of 10 mg OTC based on their expectation of approximately a 20% LDL decrease from baseline.

This specific OTC population was not studied in the 7 aforementioned studies. Nevertheless, this reviewer believes an examination of results for subjects with TC of 200-240 seems reasonable since subjects may self-select OTC use based on TC alone. To examine this subgroup, this reviewer combined the data from Studies 27201-2 and 27201-42 and evaluated the LDL response based on baseline TC (Table 2). With only 1 patient in the subgroup of interest, it is impossible to draw any conclusions regarding the LDL response to pravastatin 10 mg in patients with TC under 240.

Table 2. Week 8 LDL by baseline total cholesterol (TC) for Studies 27201-2 and 27201-42 combined

	Placebo Mean (SD)	Prav 10 mg Mean (SD)
TC 201-240		
N	6	**1**
Baseline LDL	165 (16)	**147**
% Change LDL	+14% (13)	**-4%**
TC 240-275		
N	29	25
Baseline LDL	194 (11)	192 (15)
% Change LDL	+2% (12)	-17% (10)
TC 275-300		
N	31	22
Baseline LDL	211 (14)	208 (12)
% Change LDL	+4% (11)	-20% (13)
TC 300-340		
N	39	25
Baseline LDL	242 (21)	238 (16)
% Change LDL	-5% (12)	-21% (13)
TC >340		
N	38	22
Baseline LDL	321 (57)	312 (60)
% Change LDL	+0.3% (11)	-22% (12)

In addition, this reviewer looked at LDL changes by baseline LDL subgroups (Table 3). The lowest group (139-160 mg/dl) would seemingly be the targeted group since a 20% change in LDL (the magnitude of effect the sponsor claims for the 10 mg dose) would result in values of LDL below the NCEP goal (<130). Again there are too few patients in this subgroup to draw any conclusions about the effect of the 10 mg dose on LDL's under 160.

Table 3. Week 8 LDL by baseline LDL for Studies 27201-2 and 27201-42 combined

	Placebo Mean (SD)	Prav 10 mg Mean (SD)
LDL Baseline 139-160		
N	2	**2**
% Change LDL	+23% (17)	**-3% (10)**
LDL Baseline 160-220		
N	59	48
% Change LDL	+4% (12)	-19% (10)
LDL Baseline >220		
N	82	45
% Change LDL	-2% (11)	-22% (12)

The data then from these 2 studies does not provide evidence that the 10 mg dose will reduce LDL to NCEP goal levels in the targeted OTC population.

The sponsor collected LDL data in one of their actual use studies (PREDICT). This study is described in detail by the medical reviewer and the OTC Biometrics reviewer. In PREDICT patients were randomized to OTC or prescription (RX) use of pravastatin. The dose could be titrated at the discretion of the treating physician. The Week 24 LDL results for PREDICT are shown in Table 4. The targeted OTC population showed a decrease of 13% for patients treated with 10 mg of pravastatin. (This group of 105 subjects is less than 10% of the subjects in this trial considered eligible for OTC treatment; see the medical officer's review for details regarding patient disposition in PREDICT.)

Table 4. PREDICT LDL Mean Results by Treatment Group, Total Cholesterol at baseline and Dose.

	OTC				RX			
Baseline TC	None	10 mg	20 mg	40 mg	None	10 mg	20 mg	40 mg
TC <200								
N	41	11	NA	NA	62	NA	NA	NA
Baseline LDL	103	106			110			
% Change LDL	+10%	+18%			+13%			
TC 200-240								
N	113	**105**	11	3	140	114	11	9
Baseline LDL	134	**148**	156	151	133	149	152	155
% Change LDL	+3%	**-13%**	-13%	-8%	+1%	-17%	-18%	-13%
TC >240								
N	65	117	23	6	90	161	32	12
Baseline LDL	179	170	174	179	182	171	170	179
% Change LDL	-11%	-20%	-14%	-20%	-8%	-21%	-13%	-24%

About 56% of the OTC subjects treated with 10 mg of pravastatin for 24 weeks reached the NCEP goal of less than 130 mg/dl; the percentage was higher in the subjects randomized to prescription pravastatin (68%).

Table 5. % of 10 mg subjects reaching NCEP goal of LDL<130

Baseline TC	OTC	RX
TC 200-240	56%	68%
TC >240	45%	49%

The sponsor did not submit clinical endpoint data for the OTC 10 mg dose. Previously clinical endpoint trials (Table 6) have been done using the 40 mg dose of pravastatin.

Table 6. Clinical Endpoint Trials for Pravastatin 40 mg

Study	Primary Endpoint (Risk Reduction)	Entry Criteria	Baseline Lipid Mean(SD)
WOSCOPS Primary Prevention	Time to CHD death or non-fatal MI (31%)	No history of CHD Men 45-64 yrs. LDL≥155	TC 272 (23) LDL 192 (18)
CARE Secondary Prevention	Time to death due to MI or CHD (24%)	MI w/i 3-20 mos Men+Women 21-75 yrs TC<240 LDL 115-174	TC 209 LDL 139
LIPID Secondary Prevention	Time to CHD death (24%)	History of MI or angina Men+Women 31-75 yrs TC 155-271	TC 219 (32) LDL 150 (29)

This reviewer examined the primary efficacy variable results by subgroups based on baseline TC in CARE and LIPID; two large secondary-prevention clinical endpoint studies of pravastatin 40 mg previously reviewed by this reviewer. A third large endpoint study (WOSCOPS) had no patients with TC of 200-240 (targeted OTC level). At a dose 4 times the OTC dose, clinical benefit is evident for patients with TC>200 but not with TC<200 (Figures 1 and 2).

Figure 1. Kaplan-Meier curves for the primary endpoint by baseline TC in LIPID

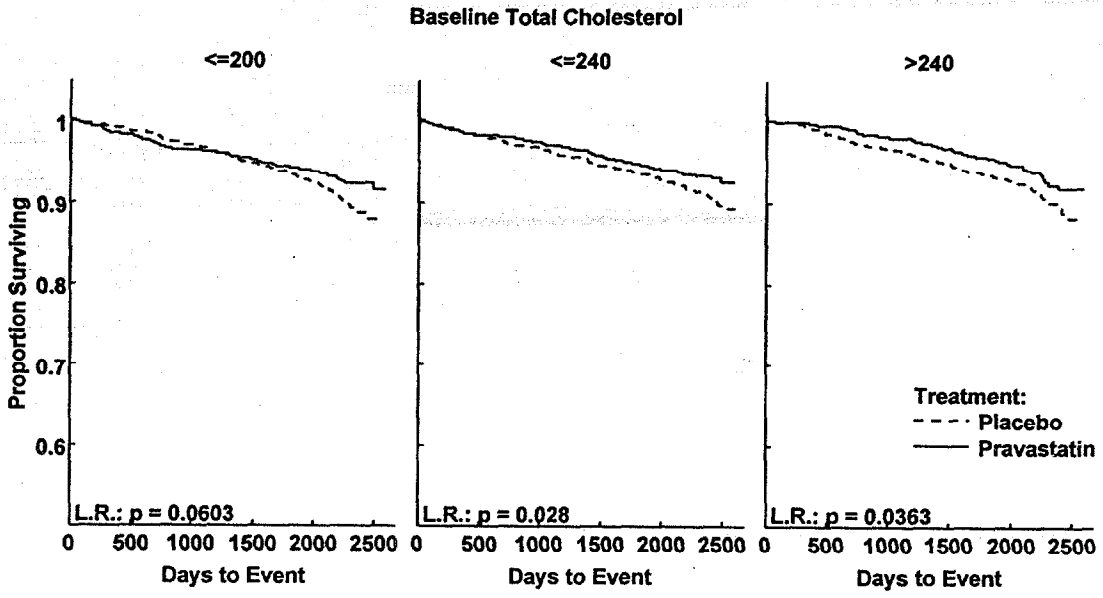
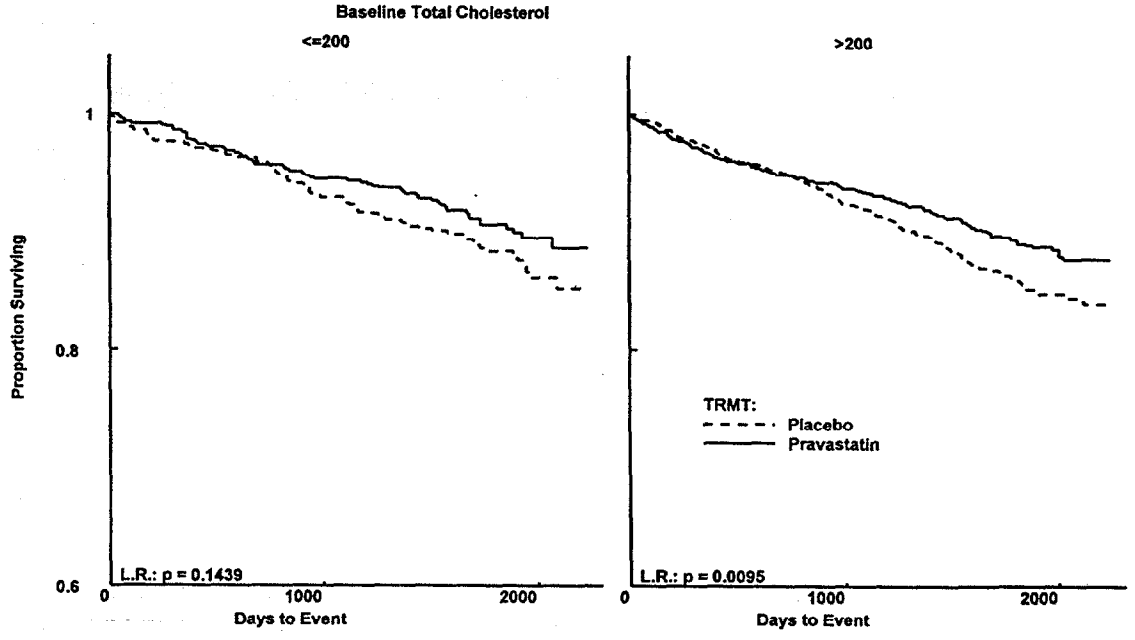


Figure 2. Kaplan-Meier curves for the primary endpoint by baseline TC in CARE



Reviewer's Overall Comments

The efficacy results from two clinical trials do not demonstrate the efficacy of the 10 mg dose of pravastatin in an OTC population since only 1 patient in these trials had a baseline total cholesterol of 200 to 240 (the level being targeted for OTC use). A significant LDL decrease of 13% was seen in subjects treated in one of the sponsor's actual use trials (PREDICT); however, less then 10% of patients eligible for OTC use actually contributed to this estimate. This reviewer concludes that there is insufficient data to establish the efficacy of 10 mg of pravastatin in an OTC population.

Clinical endpoint data is also lacking for the 10 mg dose. An examination of clinical endpoint results from 2 large secondary prevention trials of 40 mg pravastatin suggests a clinical benefit for patients with a history of CHD and TC of 200-240; these results do not extrapolate to a primary prevention OTC population being treated with 10 mg.

The clinical data reviewed here does not suggest a significant clinical benefit for patients treated with 10 mg OTC.

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HFD-715/Division 2 File, Chron, JMele, TSahlroot

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Appendix 1. Sponsor's Proposed Back Panel of OTC Package

Drug Facts

Active Ingredient (in each tablet) — **Purpose**

Pravastatin sodium, 10mg ..... Cholesterol reducer

Use

- lowers mildly elevated cholesterol.
- helps manage a risk factor for heart disease.
- to be used with a program of diet and exercise.

You have mildly elevated cholesterol if your total level is between 200-240mg/dl and your "bad" cholesterol (LDL) is over 130mg/dl.

Warnings

Do not use

- if you have liver disease or regularly drink 3 or more alcoholic beverages daily
- if you are allergic to pravastatin or any of the inactive ingredients
- if you are under 18 yrs.

Before use, ask a doctor about

- your cholesterol levels (total, LDL, HDL, triglycerides).
- your risk factors for heart disease.

Ask a doctor before use if you have any of the following conditions because you may need the prescription strength of this product:

- heart disease
- diabetes
- total cholesterol that is above 240mg/dl

Ask a doctor or pharmacist before use if you are already taking prescription medication to lower your cholesterol

Stop use and ask a doctor if

- you have any unusual muscle pain or weakness that is not caused by a cold, flu, recent injury or sprain. This is very important if you also feel weak or have a fever.

If pregnant or breast feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- take 1 tablet every day, at bed time.
- 6 weeks after starting, check your cholesterol again
  - If you have reached a healthy cholesterol level, keep taking one tablet daily to stay at a healthy level.
  - If you haven't reached a healthy cholesterol level, you may need the prescription strength of this product.
- once a year check your cholesterol level.
- continue to exercise and stay on a low-fat diet.

Other Information

- This product is very low in sodium.
- Read all product information before using.
- Keep this box and educational leaflet for important information.
- Tamper resistant inner unit. Do not use if foil seal is torn or broken.
- Do not store above 86° F (30° C). Protect from moisture and light.

Inactive Ingredients croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, povidone and red ferric oxide.

Questions or comments? Call 1-877-PRAVA10 (1-877-772-8210)
Free enrollment in Pravachol Partners Program.